

Practical Medical Mycology

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Practical Medical Mycology

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CONTENTS

Chapter	Page
I. INTRODUCTION	3
II. HUMAN INFECTIONS FROM ACTINOMYCETES.	5
✓ Actinomycosis	8
Diagnosis	8
Treatment	11
✓ Nocardiosis	12
Infections from acid-fast actinomycetes.	12
Mycetoma Pedis	15
References	17
III. COCCIDIOIDOMYCOSIS	21
IV. NORTH AMERICAN BLASTOMYCOSIS.	31
✓ V. HISTOPLASMOSIS	41
VI. SPOROTRICHOSIS	53
✓ VII. CRYPTOCOCCOSIS (TORULOSIS)	61
✓ VIII. MONILIASIS	73
IX. GEOTRICHOSIS	82
X. CHROMOBLASTOMYCOSIS	87
XI. SOUTH AMERICAN BLASTOMYCOSIS	91
XII. ASPERGILLOSIS	94
XIII. MUCORMYCOSIS	98
✓ XIV. DERMATOPHYTOSIS	103
XV. SPORES OF SAPROPHYTIC FUNGI AS ALLERGENS	119
XVI. POISONOUS FUNGI	124
Mycetismus	124
Treatment	126
Ergotism	127
INDEX	129

Practical Medical Mycology

Chapter 1

INTRODUCTION

THERE ARE MANY fungi capable of provoking disease in the human. Some of these fungi are purely saprophytic; therefore they are referred to as nonpathogenic. These fungi are capable of producing disease in man even though they do not invade the tissues of the host. Some saprophytes are poisonous, others produce airborne spores that are capable of acting as allergenic substances in a manner similar to pollens. There are other fungi that are parasitic, hence they are spoken of as pathogenic, because they invade and destroy tissue

The very nature of a mycotic infection to proceed slowly at first and then become accelerated would suggest that the causative fungi at first rely on dead or injured tissue to grow, that they have a slight inherent invasive power, and that they are able to spread only after some change has taken place in themselves or in their environment. There has not been any evidence to date that fungi increase in virulence with the progress of an infection. It is reasonable to assume, therefore, that during the course of a mycotic infection the tissues of the host become altered. This alteration in the tissues may be due to the liberation of fungus toxins, or to the development of hypersensitivity on the part of the host to the fungi or their breakdown products.

There are four classes of fungi: the Basidiomycetes, the Ascomycetes, the Phycomycetes, and the Fungi Imperfecti. The class, Basidiomycetes, comprise in part the large, fleshy fungi with compact mycelium; for example:

the mushrooms and the puffballs. There are, however, more minute forms included in this class; these are the plant parasites, the smuts, and the rusts. The Ascomycetes, the largest class of fungi, include many plant pathogens as well as molds that are of interest and importance to the bacteriologist. This class is characterized by spores that are formed in a membrane or sac called an ascus. The Fungi Imperfecti possess the characteristic mycelium of Ascomycetes, they produce spores similar to those formed by the Ascomycetes but they do not form ascospores, or at least ascospores have not been observed. The Phycomycetes are the most primitive class of fungi. They develop loose, non-septate mycelium. Common examples of this class are the species of the genera of *Mucor* and *Rhizopus*.

The molds of interest to the clinician and the bacteriologist reside, for the most part, in the class of Fungi Imperfecti. The rusts, the smuts, and the poisonous fungi of the class Basidiomycetes, the ergot fungus of the class Ascomycetes, and the species of *Mucor* and *Rhizopus* of the class Phycomycetes, are the exceptions.

Diseases caused by fungi are no longer an unimportant and remote problem in medicine and public health. Data obtained from the latest Vital Statistics Reports show that in the United States mycoses accounted for 0.56 per cent of the total deaths from infectious diseases in 1949. The number of deaths attributed to fungous infections in 1949 exceeded the total of all deaths from infections by protozoa, rickettsiae, and helminths. This trend, if not reversed, will undoubtedly assume greater importance.

Chapter 2

HUMAN INFECTIONS FROM ACTINOMYCETES

AN UNDERSTANDING of the classification of microorganisms according to their natural relationships (taxonomy) is not just an academic nicety. It gives a depth of knowledge which allows the clinician to appreciate more fully the genesis of the disease that each closely or remotely related microorganism creates. Herein has been included a key (Table 1) to the family and the genera of the order of Actinomycetales.¹ The term actinomycete is not used in a taxonomic sense, but is employed in the same manner as the terms yeast or molds might be used, and includes all of the Actinomycetales except the family of Mycobacteriaceae.

TABLE 1

THE FAMILY AND THE GENERA OF THE ORDER ACTINOMYCETALES

- A. Family MYCOBACTERIACEAE. Mycelium absent or rudimentary.
 - 1. Genus *Mycobacterium*
- B. Family ACTINOMYCETACEAE: Mycelium produced. There is disarticulation of filaments of septate mycelium into spores (arthrospores) resembling bacilli and cocci. Conidia not produced.
 - 1. Genus *Actinomyces*. Anaerobic. Not acid-fast.
 - 2. Genus *Nocardia*. Aerobic. Partially or not acid-fast.
- C. Family STREPTOMYCETACEAE. Mycelium not disarticulated. Conidia develop on proper media.
 - 1. Genus *Streptomyces*. Conidia in chains from aerial mycelium.
 - 2. Genus *Micromonospora*. Conidia not in chains, formed terminally, singly or in clusters on conidiophores.

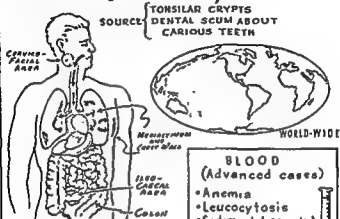
Careful study of the classification of the order of

Actinomycetales reveals that there is a close resemblance of the acid-fast actinomycetes (*Nocardia*) to the tubercle bacilli in morphology, pathogenicity, and cultural characteristics.² Of the pathogenic actinomycetes the genera of *Actinomyces* and *Nocardia* are of interest to the physician. Strictly speaking the term actinomycosis should refer only to the infections that are caused by the anaerobes *Actinomyces Israeli* and *Actinomyces bovis*. A mycosis caused by a species of *Nocardia* (aerobic and in some instances acid-fast), in the narrow sense, should be referred to as nocardiosis.

Until the appearances of the studies of Erickson,³ of England, and later Thompson,⁴ of the Mayo Clinic, it was the opinion of the majority of investigators that human and bovine actinomycosis were caused by the same aerobic microorganism, and, depending upon the investigator, the organism was referred to either as *Actinomyces bovis* or *Actinomyces Israeli*. However, since the appearance of the sixth edition of Bergey's *Manual of Determinative Bacteriology* in 1948, *Actinomyces Israeli* has been catalogued as the cause of actinomycosis in human beings and *Actinomyces bovis* as the etiologic microorganism of the bovine infection. The cultural differences of these two anaerobic actinomyces, originally described by Erickson in 1940, were subsequently supported by the findings of Thompson in 1950. Herein dogma must not be followed because it seems probable that a small number of human infections have been produced by *Actinomyces bovis* and Thompson himself, recovered one strain of *Actinomyces Israeli* from a bovine source. With the cognizance of these possible exceptions, the discussion of actinomycosis, as the disease occurs in the human, will be limited to the manifestations brought about by the invasion of the organism *Actinomyces Israeli*. A separate section under the heading of nocardiosis will deal

ACTINOMYCOSIS

ORGANISM: *Actinomyces Israeli*



SPUTUM or PUS

CULTURE

BREWER'S
MEDIA
(ANAEROBIC)



DIRECT
MICROSCOPIC



'SULFUR GRANULES'
gram-positive
(ANAEROBIC)
NOT ACID-FAST

BLOOD
(Advanced cases)

- Anemia
- Leucocytosis
- Sedimentation rate \uparrow
- Pmn. neutrophils -
% increased \uparrow



TEMPERATURE



• Irregular, spiking

DIFFERENTIAL DIAGNOSIS

- 1 Tuberculosis
- 2 Syphilis
- 3 Neoplasm
- 4 Tularemia
- 5 Osteomyelitis

- Other mycoses
 - (a) Nocardiosis
 - (b) Coccidioidomycosis
 - (c) Blastomycosis
(N & S American)
 - (d) Sporotrichosis

with infections produced by various species of the genus *Nocardia*.

ACTINOMYCOSIS

Actinomyces Israeli commonly exists as a saprophyte in the oral cavity and has never been isolated from soil or vegetation. In the mouth the organism is commonly present in and about carious teeth, dental scum, and the crypts of tonsils. From such strategic positions the organism may spread locally, giving rise to the cervico-facial type of actinomycosis, or to be swallowed to infect eventually intestines and abdominal organs, or to be inhaled or aspirated into the lungs to incite a pulmonary infection. The primary lesion of actinomycosis in man occurs most frequently in the region of the face and neck. Second and third in frequency are the primary lesions that involve, respectively, the abdominal cavity and the lungs.

Diagnosis

Clinical Picture: *Cervico-facial actinomycosis* is the commonest form of the disease and ordinarily follows neglect of carious teeth, dental extractions, fractures of the mandible, or injury to the face. From these sites the organism, that was formerly present as a saprophyte in the buccal cavity, is introduced into the tissues. The jaw bone that is so frequently involved in cattle is not as commonly affected in the human. The infection may spread to the paranasal sinuses, the salivary glands, the orbit, the neck, or the mediastinum. The skin and subcutaneous tissues of the involved site assume a swollen, woody hardness with a dusky red hue. Eventually from this chronically inflamed mass, which is riddled with intercommunicating sinuses, appear fistulous, suppurating ulcerations.

In the *abdominal type of actinomycosis* the primary

lesion frequently has its origin in the neighborhood of the appendix or cecum; consequently the symptoms of acute or subacute appendicitis are produced. From the ileocecal region the infection spreads to invade the neighboring structures, and in the female a large number of cases involving the fallopian tubes and ovaries have been reported. When the colon becomes infected the clinical picture closely resembles that of carcinoma. The primary abdominal lesions frequently are responsible for the development of secondary liver abscesses, but actinomycotic hepatic abscesses have been reported in patients without a demonstrable primary intestinal infection. Most cases of the abdominal type are eventually accompanied by chronically draining sinuses with local involvement of the abdominal muscles and subcutaneous tissues.

The primary lesions in *pulmonary actinomycosis* are usually bilateral and basal, but may occur unilaterally in any portion of the lung. From the primary site a granulomatous process is induced which usually extends to the mediastinum, pericardium and heart, and/or to the pleura producing pleural pain and occasionally pleural effusion. Eventually the organism invades directly through the pleura to the chest wall giving rise to numerous draining sinuses. Infrequently the pulmonary infection will be the result of a spread from a primary focus in one or more of the ribs. Rarely in any instance of pulmonary actinomycosis is there a spread to the regional lymph nodes, but metastasis by the blood stream does occur.

In both the abdominal and pulmonary types of actinomycosis, as the disease progresses, the patient becomes anemic, presents a leucocytosis and an elevated sedimentation rate, loses weight and strength, and has a spiking temperature with night sweats.

It has been emphasized that actinomycosis primarily

with infections produced by various species of the genus *Nocardia*.

ACTINOMYCOSIS

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In the *abdominal type of actinomycosis* the primary

substance prepared from the organism or from the broth in which the organism has been grown has never been isolated. Therefore, diagnostic skin tests and serological tests, which would be of doubtful value any way for this infection, do not exist.

Treatment

The specific measures of therapy are identical regardless of the location of the lesions. Since any therapeutic schedule must persist for months, if success is to be obtained, the choice of a drug or a combination of drugs must take into account the patient's ability to accept these medicines without concomitant allergic or noxious reactions.

Crystalline procaine penicillin^{5, 6} in aqueous suspension, in doses of 600,000 units, should be administered intramuscularly once or twice daily depending upon the severity of the infection.

For those patients who do not respond well to penicillin therapy, sulfadiazine⁷ alone or in combination with sulfamerazine, in doses of 1.0 to 1.5 grams every six hours, should be added. As soon as improvement is evident the sulfonamide dosage may be reduced to 1.0 gram, twice daily, and the penicillin discontinued.

If the infection does not respond to penicillin and/or the penicillin and sulfonamide therapy, then aureomycin,^{8, 9} 2.0 to 4.0 grams daily, or chloramphenicol,^{10, 11, 12} 750 mg every four to six hours, should be prescribed.

The iodides which apparently hasten the resorption of inflammatory tissue should be administered along with the antibacterial and antibiotic drugs. The official solution of potassium iodide should be used beginning with five drops, three times daily. This dose should be increased by two drops, a dose, a day, until the largest dosage that the patient can receive with tolerance is attained. This

involves the cervico-facial region, the abdominal cavity, and the lungs, and that the infection spreads by continuity affecting contiguous structures. Occasionally spread occurs via the blood stream, and on such occasions any part of the body may become involved. Although skin lesions are usually secondary, a few cases of primary actinomycosis involving the subcutaneous tissues have been reported. The same may be said for the endocardium.

Mycology: The diagnosis is established by isolating, from the sputum or pus, the organism in the form of characteristic "sulphur granules." These granules vary in size and shape and have a radiating lobulated structure, and are usually, though not always, yellow in color. They are best observed with a low power microscope lens; yet they are occasionally large enough to be identified with the naked eye or with a hand lens. The interior of the granule does not stand out sharply, but the clubs of the periphery are very refractile and appear as irregular lines marking the borders of the lobules. By crushing the granule between two slides and then staining with Gram's stain, the Gram positive branched filaments can be demonstrated. These branched filaments make up the interior of the "sulphur granules."

Actinomyces Israeli is difficult to culture. The pus or sputum should be washed several times with sterile normal salt solution. Suspected granules should be recovered with a bacteriological loop, washed again in sterile normal salt solution, and then placed in Brewer's thioglycolate media and incubated at 37° C. The colonies that gradually develop appear as fluffy discrete masses of variable size suspended in the media. These colonies, as they increase in size, appear dense with a finely pebbled surface. Mycelia do not project from the surface.

Skin and Serological Tests: A satisfactory antigenic

NOCARDIOSIS

ORGANISMS:

- 1 *Nocardia asteroides* - lung infection
- 2 *Nocardia madurae* } mycetoma
- 3 *Nocardia mexicana* }



SOURCE { Organisms present in soil, probably inhaled into lung, may enter foot or hand through injury

HAND FOOT } MYCETOMA, general health good.

TEMPERATURE

Irregular-spiking

BLOOD (ADVANCED CASES)

- Anemia
- Leucocytosis
- Sedimentation rate ↑
- Pmn. Neutrophils % increase ↗



S P U T U M or **P U S**
C U L T U R E
 (WASHED GRANULES)
 VEAL INFUSION
 AGAR - 1% GLUCOSE



DIRECT MICROSCOPIC



Mycelia



Granules

Aerobe; usually acid fast, gram positive

DIFFERENTIAL DIAGNOSIS (Pulmonary nocardiosis)

- | | | |
|-------------------|------------------------|--------------------|
| 1. Tuberculosis | (b) Coccidioidomycosis | (d) Sporotrichosis |
| 2. Other mycoses: | (c) Blastomycosis | (e) Cryptococcosis |
| (a) Actinomycosis | (N & S American) | |

dose should be maintained throughout the period of treatment.

Roentgen irradiation in semi-intensive dosages, administered only by a specialist, should accompany antibacterial, antibiotic, and iodide therapy.

The wisdom of surgical incision and/or excision must be left to the judgment of the attending physician and surgeon, either after or before adequate medical treatment has been given a trial. If there are incised lesions or sinus tracts, they should be irrigated daily with half-strength Lugol's solution, or 1 per cent aqueous solution of gentian violet.

Non-specific measures of treatment are as important for the patient with actinomycosis as they are for the patient with any other chronic infection. There must be prolonged bed rest; long-headedness in the administrations for restlessness and insomnia; provision of a simple, nutritious diet adequate in calories and vitamins; prevention of dehydration by supplying an adequate fluid intake, and vigilance to the care of the mouth, bowels, urinary bladder and skin.

NOCARDIOSIS

In this section the term nocardiosis has been reserved to define infections in man caused by one or several of the species of actinomycetes included under the genus *Nocardia*. The discussion will be divided into two sub-headings: (1) infections caused by the acid-fast actinomycetes; (2) infections caused by the species of *Nocardia* that are responsible for the clinical picture, mycetoma pedis.

1. Infections from Acid-fast Actinomycetes

Although infections caused by these organisms are not common in man, they are of considerable interest scien-

cent glucose, *Nocardia asteroides* grows aerobically and forms a wrinkled mealy growth bearing close resemblance to the growth of the tubercle bacillus. The organism is acid-fast though this characteristic is not so pronounced as in the tubercle bacillus. In general, *Nocardia asteroides* is more definitely acid-fast in tissues and exudates than in cultures, and the acid-fastness tends to be lost after continued cultivation.

Although *Nocardia asteroides* grows readily on ordinary culture media, the growth is slower than bacteria and their isolation from sputum by plating is difficult. The procedure of choice for establishing a diagnosis of nocardiosis is by guinea pig inoculation. With this technique pure cultures can be obtained. Following the intraperitoneal inoculation of guinea pigs the animals usually die in four to nine days. At autopsy characteristic milary white nodules are observed over the omentum and the peritoneal surfaces.

2. Mycetoma Pedis (Madura Foot)

In 1862, Carter,³ of Bombay, India, proposed the term mycetoma to describe a fungous infection characterized by a localized enlargement of the foot. This infection was frequently seen in India and was popularly spoken of as Madura foot. Although this infection is included under nocardiosis, it is necessary to state that the infection may be caused by fungi (hyphomycetes or ascomycetes) unrelated to the actinomycetes.⁴ The infection may occur throughout the World, but is most common in tropical and subtropical countries in individuals who do not wear shoes, and who are, therefore, more exposed to trauma.

Diagnosis

Clinical Picture: The clinical appearance of a typical case is distinctive. The lesion is nearly always on the foot,

tifically because the organisms form a connecting link between the bacteria and the higher fungi. The actinomycete in this group of interest to the clinician is *Nocardia asteroides*, which may be distinguished from *Actinomyces Israeli* and *Actinomyces bovis* by the readiness with which it is cultivated on artificial media, and by its high virulence for the guinea pig.

Nocardia asteroides is common in soil,¹ and it is reasonable to contend that pulmonary infection is initiated by the inhalation of contaminated dust particles. Although this actinomycete has many characteristics similar to the tubercle bacillus, there has been no concrete evidence that the two organisms are immunologically related. Cross reactions between tuberculin and asteroidin, which is a filtrate prepared from broth cultures of *Nocardia asteroides*, have not been demonstrated experimentally in infected guinea pigs and rabbits.

Diagnosis

Clinical Picture: In the lung² the organism produces a caseating type of bronchopneumonia that may be followed by cavity formation. The clinical picture, therefore, may be easily confused with that of pulmonary tuberculosis. There is a tendency for the organisms to disseminate through the blood with the resulting formation of abscesses in many of the organs, especially the brain. Death is frequently caused by a brain abscess, and quite often pulmonary lesions are not discovered until post mortem. Pulmonary nocardiosis is difficult to differentiate from pulmonary tuberculosis. The actinomycete undergoes fragmentation in the sputum, and being acid-fast the fragments resemble tubercle bacilli. However, the fragments are variable in length and if the sputum is examined carefully long branched filaments will be found.

Mycology: On veal infusion agar containing 1 per

sulfamerazine, and aureomycin are the drugs of choice.⁶

In regard to mycetoma pedis, amputation of the affected extremity is advisable only after all medical measures have proved ineffective.

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but may occur at times on the hand.⁵ Rarely are other regions of the body involved. There is marked swelling and destruction of the tissues (sometimes including bone) with the formation of suppurating fistulae. Granules similar to "sulphur granules" may be isolated from pus. In the infections produced by *Nocardia* species the granules are usually white or yellow and may vary in size from that of a pin-point to 3 or 4 millimeters. The infection tends to remain localized, though in rare instances there is an extension up the leg or the arm via the lymphatics. There is no tendency to spread to other parts of the body and rarely is life endangered.

Mycology: The species of *Nocardia* causing mycetoma are to some extent geographically limited. *Nocardia madurae* is more common in southeastern Asia and the Pacific Islands, while *Nocardia mexicana* is isolated more frequently in the southern portion of the United States and in Mexico. It may be assumed that these fungi ordinarily grow in the soil or on dead vegetation, and become pathogenic only when they are introduced by accident into the subcutaneous tissues. In all cases of mycetoma the fungus usually forms granules or small colonies in the tissues, and these granules are composed of densely packed, delicate, radiating hyphae. The granule may be either yellow or white in color. On agar *Nocardia madurae* forms a wrinkled grey colony which, in some instances, is covered with short, white, aerial hyphae. *Nocardia mexicana* forms deep and folded colonies spreading profusely over the surface of the agar.

Treatment

The specific and non-specific measures of treatment are similar to those for actinomycosis. There is one exception of notable importance. Penicillin is less effective in nocardiosis. Sulfadiazine, alone or in combination with

NOCARDIOSIS

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COCCIDIOIDOMYCOSIS

ORGANISM *Coccidioides immitis*

B L O O D

- Sedimentation rate $\uparrow \uparrow \uparrow$
- Leucocytosis
- Eosinophiles-% increase \uparrow

S E R O L O G Y

- Precipitins 2 Severe infection POS
- C.F. Antibodies 3 Post-recovery-NEG.
- 1 Mild infection-NEG

SKIN TEST • Positive

S P U T U M

DIRECT MICROSCOPIC



"SPHERULES"

CULTURE (SABOURAUD'S)



Mycelium Arthrospores
CHLAMYDOSPORES

DIFFERENTIAL DIAGNOSIS

- | | |
|----------------|------------------|
| 1 Common cold | 5. Poliomyelitis |
| 2 Influenza | 6 Scarlet fever |
| 3 Pneumonia | 7. Measles |
| 4 Tuberculosis | 8 Drug eruption |
- IF PROFOUND MORBILLIFORM RASH APPEARS

S E R O L O G Y

- Precipitins
 - C.F. Antibodies
- both present in high titers

S K I N T E S T

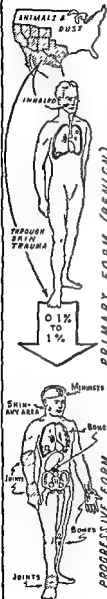
- Positive (often negative in terminal phase)

DIFFERENTIAL DIAGNOSIS

- 1 Tuberculosis
- 2 Encephalitis (if meningeal symptoms appear)

PRIMARY FORM (BENIGN)

PROGRESSIVE FORM



Chapter 3

COCCIDIOIDOMYCOSIS

Coccidioides immitis, a fungus whose taxonomic position is still revocable, produces an acute, usually mild and benign respiratory infection, which is classified as the primary type of coccidioidomycosis. Infrequently the infection becomes chronic, and then disseminates to almost any organ producing, therein, granulomatous lesions which progress to such an extent that one out of two individuals so affected eventually succumb. This chronic form of the disease is spoken of as the progressive or disseminated type of coccidioidomycosis.

Provincialism has unfortunately crept into the nomenclature employed for describing the various clinical expressions of coccidioidomycosis. This jargon, though no longer excusable, is easily reconciled when one considers that originally in this country the fungus and the disease were believed confined to the region of the San Joaquin Valley, and adjacent deserts, in the state of California. Though the endemic areas in North America now encompass most of southwestern United States and northern Mexico, the regional names of the California endemic sites are still fondly, but lamentably, used in describing the various clinical entities of this infection.

When the skin lesions of erythema nodosum and erythema multiforme have occurred with the primary form of the infection, the illness has been described as San Joaquin fever, valley fever, or desert fever. When the symptoms of arthralgia are added, the disease has been referred to as desert rheumatism. To make matters even

COCCIDIOIDOMYCOSIS

ORGANISM *Coccidioides immitis*

B L O O D

- Sedimentation rate $\uparrow \uparrow \uparrow$
- Leucocytosis
- Eosinophiles-% increase \uparrow

S E R O L O G Y

- Precipitins 2 Severe infection-POS
- C F Antibodies 3 Post-recovery-NEG.
- 1 Mild infection-NEG.

SKIN TEST • Positive

S P U T U M

DIRECT MICROSCOPIC



"SPHERULES"

CULTURE (SABOURAUD'S)



CHLAMYDOSPORES

DIFFERENTIAL DIAGNOSIS

- | | | |
|----------------|-----------------|--|
| 1 Common cold | 5 Poliomyelitis | } IF PERIPHERAL
MORBILLIFORM
RASH
APPEARS |
| 2 Influenza | 6 Scarlet fever | |
| 3 Pneumonia | 7 Measles | |
| 4 Tuberculosis | 8 Drug eruption | |

S E R O L O G Y

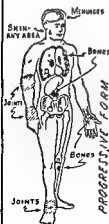
- Precipitins } both present in
- C.F Antibodies } high titers

S K I N T E S T

- Positive (often negative in terminal phase)

DIFFERENTIAL DIAGNOSIS

- 1 Tuberculosis
- 2 Encephalitis (if meningeal symptoms appear)



which are readily adapted to widespread dissemination, gain entrance into the human body through the respiratory tract or less frequently into the skin following trauma. It has been proposed that rodents and other animals in the endemic areas act as reservoirs for the fungus.¹⁰ Most coccidioidal infections are completely asymptomatic; however, symptomatic or asymptomatic, immunity is conferred on individuals following recovery.¹¹

*The symptoms of primary coccidioidomycosis*¹¹ are indistinguishable from those of many acute, mild respiratory infections; yet there may be all gradations in symptomatology from mild infections to very severe prostrating illnesses. The incubation period varies from one to three weeks. There is usually fever which ranges from 99° to 101° F. Chills occur only with a higher temperature level. Cough may or may not be present. Pain in the chest is one of the most typical and suggestive symptoms of the disease. The character of the pain varies from a sensation of tightness to sharp knife-like seizures which tend to stop respiration. Headache, backache, night sweats, anorexia, and sore throat are common symptoms. Very often a morbilliform rash will appear one to two days after the onset of the infection.

The physical findings referable to the lungs are usually not abnormal, but in one out of five patients some change in the quality of the breath sounds is detected. Eight to 14 days following the onset of the illness hypersensitive reactions may occur; namely, erythema nodosum¹⁰ and/or erythema multiforme (2 to 5 per cent of patients), arthralgia (25 per cent of patients), and phlyctenular conjunctivitis. Roentgenograms of the lungs may or may not reveal thin-walled cavitation usually present in the middle or lower lobes, but rarely above the clavicle; soft infiltrations, enlarged hilar nodes; fan-shaped densities radiating out from the hilar nodes.

worse, the above names have been employed to describe any primary type of coccidioidomycosis even though skin lesions and joint manifestations are absent, simply because coccidioidomycosis is difficult to pronounce. The progressive form of the infection is also spoken of as coccidioidal granuloma, the San Joaquin Valley disease, or just, the California disease. The protozoan infection, coccidiosis, must not be confused with coccidioidomycosis.

The first case of what we now recognize as the progressive form of coccidioidomycosis was reported by Posadas¹ and Wernicke² from the Chaco region of Argentina in 1892. Rixford³ reported a similar case from California, the first in North America, two years later. Then Rixford with Gilchrist⁴ made a careful study of the disease and decided that the infection was caused by a sporozoan and, because of its resemblance to the coccidia, named the organism, *Coccidioides*. Ophuls and Moffitt⁵ finally proved in 1900 that *Coccidioides* was a fungus and not an animal parasite.

Not until 1936 was the primary form of the infection recognized. In that year Gifford⁶ described *Coccidioides* as the cause of San Joaquin fever. But it remained for Dickson,^{7, 8, 9} one year later, to drive the message home to physicians, and it was he who proposed that coccidioidomycosis be designated to include all manifestations of the primary and the progressive forms of the infection caused by the fungus, *Coccidioides immitis*.

Diagnosis

Clinical Picture: *Primary or initial coccidioidomycosis.* This form of the infection occurs by the tens of thousands in the arid and semi-arid regions of southwestern United States. The fungus is present in the dust and soil of these areas. The light minute arthrospores,

velop into the progressive form of coccidioidomycosis, which is a chronic, malignant, disseminated disease involving the cutaneous, subcutaneous, visceral and bony tissues. Dissemination occurs more frequently in the Mexican, the Filipino, and the North American negro races, than in the North American white race. The highest rate of dissemination takes place in the pregnant female,¹² particularly when the infection is acquired during a late stage in gestation.

The symptomatology of the progressive infection depends entirely upon the site to which the fungus has migrated. If lung infiltrations present in the primary form persist for six or more weeks a progressive form of the disease should be suspected. With progression of the infection the infiltrations increase in size, there is enlargement of the mediastinal glands; cavities, formerly present, enlarge; the cough is pronounced; the sputum which was scanty becomes more profuse and is occasionally tinged with blood.

If the progressive form of the disease is suspected the entire skeleton should be x-rayed. Typical lesions in the bones appear as sharply circumscribed areas of destruction with scarcely any reaction in the surrounding bone. Although any bone in the body may become involved, the ribs, the vertebrae, the small bones of the hand, and the tibia are most frequently invaded in the order named. Dissemination also affects the joints, and involvement of the ankle joint for an unknown reason commonly occurs. The wrists and the elbow joints are next most frequently affected in the order enumerated. In white patients meningitis occurs and the course simulates that of tuberculous meningitis. In the dark skin races there is more of a tendency toward the development of subcutaneous and joint abscesses. Verrucous skin lesions are common in the fulminating cases. These may appear on the face, scalp, ex-

Laboratory studies are helpful in establishing a diagnosis. There is frequently, though not always, a leucocytosis which is moderate in degree (10,000 to 16,000). Ordinarily a preponderance of immature leucocytes is observed along with an eosinophilia ranging between 4 to 20 per cent or higher. In the healing stages, the proportion of the lymphocytes rises to 50 per cent of the total white blood cells. Therefore, because the differential count does have some prognostic value, repeated hematological examinations should be made during the course of the disease. The sedimentation rate is always elevated in the active phase of the infection and returns to normal as the illness subsides.

The *coccidioidin skin test* ¹² is usually positive in mild as well as severe infections. A 1:100 dilution of coccidioidin is employed for routine skin testing. Dilutions of 1:1,000 or 1:10,000 should be used in patients with erythema nodosum or erythema multiforme. If a very large skin reaction, to the point of being uncomfortable to the patient, should occur there is no danger of lighting up a quiescent focus. However, there may be a systemic reaction and even recurrence of erythema nodosum without a permanent deleterious effect.

The *sedimentation rate* is of value in interpreting the significance of the coccidioidin skin test. Should a positive skin test occur in a patient with a normal sedimentation rate it is unlikely that the current illness is coccidioidal. On the other hand an elevated rate does not establish with surety that the infection is currently active, but it does point to the fact that the possibility exists. Precipitins and complement-fixating antibodies are usually absent in mild infections but are present in severe infections.

Progressive or disseminated coccidioidomycosis. Approximately 0.1 to 1.0 per cent of the primary cases de-

Treatment

There is no specific form of therapy. Every type of chemotherapeutic agent has been employed but the efforts have been more or less random. Early reports of "prolongation" of the disease were obtained but the most pronounced by Sargent and others was limited to the fungistatic and fungicidal action of the *Amphotericin B* in patients with *Coccidioides immitis* in culture in 1955, 56, and 57. 58. 59. 60. Unfortunately the results of these studies are

Therapy at this time must be symptomatic, and it can only be hoped that by continuing appropriate measures carefully, that progression and dissemination of the infection can be prevented. The patients with progressive coccidioidomycosis must be kept at constant rest and (a) the physical findings of the infection have disappeared, (b) there is evidence from roentgen examination of the lungs that the lesion has either disappeared or is regressing; (c) the sedimentation rate has returned to normal, and (d) the progressive and complement-fixing antibodies are disappearing or stable. If cavitation exists in the primary focus of the disease and has not disappeared or healed within three to six months, or if repeated hemorrhages have occurred from the cavity, the lesion should be resected. The floors and walls of the rooms or wards housing patients should be washed periodically with lysol, to prevent growth of the fungus in cracks and crevices.

Most of the patients with the progressive form of the disease die in three to 12 months, but some may recover spontaneously. If the patient is markedly sensitive to coccidioidin, that is gives a large skin reaction to a 1:1,000 or 1:10,000 dilution, then immunization with this antigen should be given a trial.¹⁶

tremities or trunk, and usually signify miliary dissemination. Generally speaking, the progressive form of coccidioidomycosis mimics tuberculosis.¹⁴

The *coccidioidin skin test* is ordinarily positive, but may become negative in the terminal stages just as the tuberculin skin test becomes negative in the last stages of tuberculosis. The precipitins and complement-fixing antibodies are present in high titers.

Mycology: The organism, *Coccidioides immitis*, exhibits marked dimorphism. It grows on Sabouraud dextrose as a white cottony mold which pigments with age. Old cultures contain myriads of large thick-walled spores (chlamydospores). These spores, which are particularly adapted for maintaining vitality through long periods of dormancy, are the infective form of the fungus that occurs in nature. When these spores are injected into animals they enlarge and become spherical. These spherical cells, referred to as "spherules," give rise to endospores by cleavage of their cytoplasm. The endospores escape when the wall of the "spherule" ruptures, hence to repeat the parasitic phase of the life cycle. The "spherule" that is found in the sputum of the patient infected with *Coccidioides immitis*.

It is generally taught that the "spherules" are not contagious. This is based upon the fact that there is no evidence of man to man transmission of the disease. However, Rosenthal,^{15, 16} of Chicago, demonstrated that guinea pigs may contract the disease following tracheal inoculation of the "spherules," and that healthy normal animals housed with animals suffering from pulmonary lesions may develop gross pulmonary lesions and other signs of infection. Therefore, one is tempted to remain cautious in accepting the old dogma that coccidioidomycosis is never contagious.

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Chapter 4

NORTH AMERICAN BLASTOMYCOSIS

BLASTOMYCOSIS, the North American type, is a relatively common fungus disease characterized by the formation of granulomatous lesions in various regions of the body. There is a marked predilection for involvement of the skin, lungs, and bones. Although the greatest concentration of cases in the United States occurs in the southeastern states and in the Mississippi River Valley area, isolated cases have been reported from nearly every section of the United States as well as regions in eastern and western Canada.¹

Dr. T. C. Gilchrist,^{2, 3} a dermatologist of Baltimore, Maryland, first described the disease and later named the causative fungus, *Blastomyces dermatitidis*. The fact that Gilchrist was primarily interested in cutaneous medicine is manifested by the appendage which he coined for the genus, *Blastomyces*. Actually the name blastomycosis is doubly a misnomer. It was first thought that the causative organism was a true yeast, and secondly that *Blastomyces* was the proper scientific name for the yeasts. However, the organism is not a true yeast and, on the other hand, *Saccharomyces* is the proper name for the yeasts.

Blastomycosis is not spread from man to man but is derived from some source in nature, probably soil, where the fungus survives and multiplies. Infections may develop in patients of any age, but the disease does occur nine times as frequently in adult males as in adult females. The marked predilection for males is undoubtedly accounted for by the fact that it is they, rather than the females, whose occupations take them into the fields and





NORTH AMERICAN BLASTOMYCOSIS

ORGANISM:

Blastomyces dermatitidis

BLOOD

- Anemia - advanced cases
- Leucocytosis
- Sedimentation rate 
- Pmn. neutrophils per cent increase 



TEMPERATURE

- Irregular-spiking.



SKIN TEST (*Blastomyces* vaccine)

- Delayed in type and usually positive.

SEROLOGY complement-fixation test (Antigen-pulverized cells of tissue phase.)

- Result-titer low, rises with progress of infection



SPUTUM or PUS

CULTURE

Blood agar
(37°C)



Sabouraud's
(Room temp)



PUS

DIRECT MICROSCOPIC



DIFFERENTIAL DIAGNOSIS

- 1 Tuberculosis
- 2 Syphilis
- 3 Neoplasm
- 4 Sarcoidosis
- 5 Silicosis
- 6 Osteomyelitis

- 7 Other mycoses
- a Coccidioidomycosis
- b Actinomycosis
- c Cryptococcosis
- d Sporotrichosis
- e Moniliasis

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forests, where contact with the natural source of the saprophytic form of the fungus is initiated.

Diagnosis

Clinical Picture: The infection may begin primarily in the skin and remain localized there for months or years before it spreads to the internal organs. In the majority of cases, the primary lesion appears on the skin of the face, hands, wrists, or forearms. A firm papule first appears, and about this a number of secondary nodules develop, which gradually enlarge and coalesce. These lesions break down and discharge purulent material from their centers. As the lesion progresses there develops a large elevated mass of tissue with an irregular ulcerated surface that resembles a tuberculous ulcer. Healing occurs first in the central portion of the lesion and is followed by the formation of scar tissue.

Most cases of *systemic blastomycosis* begin with pulmonary infection. The onset is insidious and the symptoms are those of an ordinary, subacute respiratory infection. There is usually an unproductive cough, discomfort in the chest, low-grade fever, and slight shortness of breath. As the infection progresses the shortness of breath becomes more annoying, the temperature climbs, and there is loss of weight and strength. Roentgenograms of the lungs frequently disclose enlargement of the mediastinal lymph nodes. Dense masses are frequently observed near the hilum and project into the lung fields with irregular outlines. The finding of such a hilar mass may quite naturally provoke a diagnosis of bronchogenic carcinoma. In the latter stages of the disease the mediastinum may be invaded; involvement of the pericardium and heart soon follows.

The infection may disseminate from the lungs by way of the blood stream, and when disseminated blastomy-

cosis is suspected a roentgen examination should be made of the entire skeleton. The ribs and vertebrae are the most frequently involved of all the bones, and the vertebrae if totally destroyed will collapse and cause compression of the spinal cord. It is difficult to differentiate the bony lesions of blastomycosis from those of coccidioidomycosis and actinomycosis. The abdominal viscera also become involved in the disseminated form of the disease with abscesses forming in the liver, spleen, and kidneys. As the disease progresses the sedimentation rate becomes elevated. There is also an hypochromic anemia, and a leucocytosis with an increase in the percentage of polymorphonuclear leucocytes.

Mycology: The diagnosis is established by demonstrating the organism in pus or sputum. In the body tissues the fungus occurs only as a round or oval yeast-like cell which reproduces by budding. These cells are easier to demonstrate if the material for examination is first treated with 20 per cent sodium hydroxide. The finding of doubly contoured budding cells with granular contents and which in size are slightly smaller than leucocytes makes the diagnosis certain. Cultures should be made on both Sabouraud's and blood agar media. On Sabouraud's glucose agar at 30° C the colonies first appear smooth and greyish, but they soon become wrinkled and eventually a white cottony type of growth develops. Cultures on blood agar incubated at 37° C. do not develop filamentous growth, but remain yeast-like in appearance.

Skin and Serological Tests: A heat-killed suspension of the yeast phase of blastomyces is used as skin testing material.⁴ The organism is grown at 37° C. on beef infusion glucose agar. The cultures are washed from the slants with sterile normal salt solution, and a 1 ml sample is then centrifuged in a Hopkins' tube at 2,000 rpm. for 15 minutes. The stock vaccines are then diluted 1:1,000

according to the serial volume reading of the 1 ml. sample in the Hopkins' tube. The 1:1,000 dilutions of vaccines are heat-killed by placing them in a water bath at 56° C. for two hours. Tests are made for sterility, and then sufficient phenol is added to make a 0.5 per cent concentration. Skin tests are performed by injecting intradermally 0.1 ml. of the vaccine suspension just described. The skin test is read and interpreted exactly as a tuberculin test.

A broth filtrate⁵ (blastomycin) of the growing organism may also be employed for skin testing. This filtrate is prepared in a manner similar to histoplasmin and coccidioidin.

Skin tests are usually negative in the initial stages of the infection and may also be negative in the terminal phase of the disease. Cross reactions with *Blastomyces* vaccine or blastomycin, and histoplasmin and coccidioidin are common. This is probably due to an antigenic fraction common to *Blastomyces dermatitidis*, *Histoplasma capsulatum* and *Coccidioides immitis*. For this reason skin tests with *Blastomyces* vaccine or blastomycin, histoplasmin, and coccidioidin should always be made despite the mycotic infection suspected. Only those patients very sensitive to coccidioidin (positive reaction to 1:10,000 dilution) give cross reactions with *Blastomyces* vaccine or blastomycin, and histoplasmin. Cross reactions between *Blastomyces* vaccine or blastomycin, and histoplasmin are very common. However, patients with blastomycosis give larger reactions to *Blastomyces* vaccine or blastomycin, than to histoplasmin, and the reverse is true of patients with histoplasmosis.⁶

The complement-fixation test for blastomycosis was introduced by Dr. Donald S. Martin,^{7, 8} of Duke University. The antigen is prepared by pulverizing the cells of the tissue phase of the organism. The complement-fixating antibodies are not stimulated by mild clinical infec-

tions or, at least if they are present, they cannot be detected by present day methods. A positive complement-fixation test indicates active infection and the titer rises as the infection progresses. The titer also declines as the patient improves, and disappears after recovery.

Treatment

Cutaneous blastomycosis without allergy, as demonstrated by a negative skin test to either *Blastomyces* vaccine or blastomycin, usually heals in a few months following treatment with iodides and x-ray. The official solution of potassium iodide is administered by beginning with five drops, three times a day, after meals, and increasing each dose one drop a day until tolerance is reached, or until the patient is receiving 50 drops, three times a day. This latter optimum dose, or the largest dose tolerated, should be continued until recovery. X-ray therapy should be given in doses of 75 to 100 roentgens at seven to 10 day intervals. Usually a total dosage of 1,500 roentgens is sufficient. If the cutaneous lesion is small and readily accessible, surgical removal is justified.

Cutaneous blastomycosis with allergy, as manifested by a positive skin test to *Blastomyces* vaccine or blastomycin, does not respond to iodides and x-ray until desensitization with a stock or autogenous *Blastomyces* vaccine has been accomplished. Following a period of desensitization the lesions heal as readily and as completely as those present in the non-allergic patient.

Before discussing the management of pulmonary and systemic blastomycosis some consideration must be given to the technique of desensitization therapy. In the first place there is no stereotyped schedule of desensitization that is applicable for all patients, either for those with cutaneous, or those with pulmonary, or systemic blastomycosis. The method of preparing *Blastomyces* vaccine

and the dosage for skin testing has already been discussed. This same vaccine as used for skin testing should be diluted 10, 100, 1,000 or more times, until one ascertains the strength of vaccine that fails to produce a positive skin test after 0.1 ml. has been injected intradermally. Treatment is then instituted with 0.1 ml. of this dilution given subcutaneously, and each subsequent dose is increased by 0.1 ml. Treatment is given every 72 hours, and finally when a dose of 1 ml. has been reached the procedure is repeated, beginning with 0.1 ml. of the next lowest dilution, and so on until 1 ml. of undiluted vaccine is administered. This latter dosage is continued at weekly intervals throughout the entire course of the patient's illness. If local reactions, manifested by swelling and redness at the site of administration 12 to 24 hours after injection, should occur the dose should be reduced, and the largest dose which just fails to produce a local reaction is maintained at weekly intervals without further attempt to increase the dosage.

Pulmonary and systemic blastomycosis is not often favorably improved after x-ray therapy. Patients in good general condition with sera containing complement-fixating antibodies usually respond to iodide therapy. Iodides should be administered in a manner similar to that described in the section dealing with the treatment of cutaneous blastomycosis, and should be given until recovery. Improvement is very gradual; hence therapy must be carried out over a period of from one to three years. Those patients with disseminated systemic blastomycosis who have a fairly high titer of complement-fixating antibodies and negative skin tests usually die within two to three months. This group is neither aided by iodides nor vaccine therapy. The patients with positive skin tests with or without concomitant complement-fixating antibodies usually fail to respond to iodides, and their disease be-

comes rapidly fatal following the use of iodides. However, if these patients are desensitized with *Blastomyces* vaccine and then treated with iodides they ordinarily improve as rapidly as those patients who were not allergic. Those patients without complement-fixating antibodies and with negative skin tests should receive immunizing doses of *Blastomyces* vaccine until there is evidence of the stimulation of complement-fixating antibodies. Thereafter, iodide therapy should be given.

On the basis that certain of the diamidines exert an *in vitro* fungistatic effect on *Blastomyces dermatitidis*, several patients with blastomycosis have been treated with some success with stilbamidine⁹ and propamidine.^{9, 10} Stilbamidine, 0.05 gm. in 100 ml. of 5 per cent glucose solution, is given by slow intravenous drip the first day. If this dose is well tolerated then 0.1 or 0.15 gm. is administered in a similar fashion every day for 10 to 14 days. This course may be repeated, if advisable, after a two weeks rest period. The amount of stilbamidine necessary for cure is not known, but probably a total dosage of 3 to 6 gm. administered in two or three courses is sufficient.^{10, 11, 12, 13, 14, 15, 16}

In a high percentage of patients, two to five months after treatment with stilbamidine, a neuropathy involving the trigeminal nerve appears. The sensation to touch is lost, yet the sensation to pain, temperature, and pressure remain intact. The sensory changes may persist indefinitely.

A 0.1 per cent solution of propamidine prepared in a 5 per cent glucose solution may be applied locally to surface lesions, or injected into fistulae daily or every other day.

Although the use of stilbamidine is the first drug of choice in the treatment today of all cases of pulmonary and systemic blastomycoses, regardless of the immuno-

logic and allergic status of the patient, physicians must be ever mindful that its use represents a new form of treatment and, therefore, its dangers and limitations have not at this time been entirely evaluated

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HISTOPLASMOSIS

ORGANISM

Histoplasma capsulatumCONTAMINATED
DUST ORGANISM
INHALEDFIRST STAGE
(INFILTRATION)SECOND STAGE
(CALCIFICATION)BENIGN TYPE
(SYMPTOMATIC OR
ASYMPTOMATIC)

SKIN TEST

Tuberculin: *Negative*Histoplasmin: *Positive*PRIMARY
MUCO-CUTANEOUS TYPESPUTUM; BLOOD; URINE; FECES
BONE-MARROW, LYMPH NODE

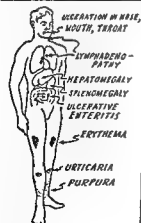
DIRECT MICROSCOPIC

MARROW,
BLOOD,
LYMPH
NODE

SPUTUM

YEAST-
LIKE
CELLS

MONOCYTE

ULCERATION IN NOSE,
MOUTH, THROATLYMPHADENO-
PATHY

HEPATOMEGALY

SPLENOMEGALY

ULCERATIVE

ENTERITIS

ERYTHEMA

URTICARIA

PURPURA

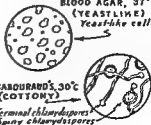
DISSEMINATED TYPE

CULTURE

BLOOD AGAR, 37°C

(YEASTLINE)

Yeast-like cells

SABOURAUD'S, 30°C
(COTTONY)Terminal chlamydospores
Spiny chlamydospores

Chapter 5

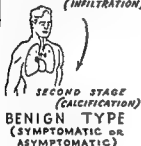
HISTOPLASMOSIS

THE CLASSIC AND fatal type of histoplasmosis, with its widespread involvement of the reticuloendothelial system, depression of blood elements, irregular fever, and emaciation, was first described by S. T. Darling¹ from the Panama Canal Zone in 1906. Darling observed a relatively large encapsulated (capsule now known to be an artefact²) organism in tissues that was similar in size and shape to the etiologic agent of kala azar. He believed this organism to be a protozoan and gave it the name *Histoplasma capsulatum* and the resulting disease, histoplasmosis. De Monbreun³ in 1934 cultured and cultivated the microorganism on Sabouraud's medium and established that it was a fungus and not a protozoan. De Monbreun then proposed to change the name of the organism and the disease because of Darling's misconception, but since Darling had created a new generic and a new specific name for the parasite, De Monbreun's objections were held invalid and the names originally proposed by Darling were maintained. In 1939 De Monbreun⁴ suggested that a relatively mild and non-fatal form of the disease might exist, which was similar in nature to the primary and non-fatal form of coccidioidomycosis. The epic work of Palmer⁵ and that of Christie and Peterson⁶ ensued, and it was they who were principally responsible for the discovery and recognition of the common benign pulmonary type of histoplasmosis.

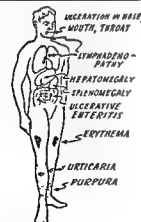
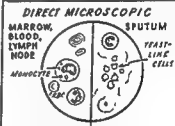
There was a tendency at first to believe the disease to be endemic in the states bordering the Mississippi River

HISTOPLASMOSIS

ORGANISM

Histoplasma capsulatum

SKIN TEST

Tuberculin: *Negative*Histoplasmin: *Positive*SPUTUM; BLOOD; URINE; FECES
BONE-MARROW, LYMPH NODE

DISSEMINATED TYPE

CULTURE

BLOOD AGAR, 37°C

(YEASTLIKE)

Yeast like cells

SABOURAUD'S, 30°C
(COTTONY)Terminal chlamydospores
Spiny chlamydospores

the histoplasmin skin test is strongly positive, and the tuberculin test is negative or only mildly positive.

In the *symptomatic pulmonary form* of histoplasmosis the clinical course of the disease and the roentgenologic findings offer a relatively uniform picture. The onset is sudden, after an incubation period of five to 18 days, with the symptoms of generalized malaise, weakness, vague chest pain, nonproductive cough and fever (102° to 105° F.). There is a paucity of positively pertinent physical findings. During the first few days of illness the roentgenogram of the lungs is unrevealing, but later disseminated and bilateral lesions varying from fine, mottled, granular infiltrations, to soft, miliary nodules are observed. Cavitation occurs rarely. The lesions tend to calcify in three to five years from the onset of the acute illness. Even after the acute phase of the illness has disappeared many of the patients persist for months or even years with symptoms of dyspnea, cough, and abnormal fatigue.

There is some indication that the symptomatic form of the pulmonary infection may occur in epidemics. There is, in this regard, the instance of 26 soldiers who developed a severe pneumonitis after seeking refuge from a storm in a cellar while on maneuvers at Camp Gruber, Oklahoma.¹⁵ *Histoplasma capsulatum* was isolated from the soil of this cellar; accordingly, with this bit of evidence and the results of studies carried out subsequently on the afflicted soldiers, it was concluded that their pneumonitis was due to *Histoplasma capsulatum*. Likewise, 23 men developed "acute miliary pneumonitis" after shoveling pigeon manure from an old schoolhouse in Plattsburg, New York,¹⁶ and another 12 men contracted a "pneumonitis of unknown etiology" following the shoveling of pigeon manure from a basement of a water tower in Cincinnati, Ohio.¹⁷ In each of these two epi-

and its larger tributaries. In this area Emmons⁷ in 1949 and Ajello and Zeidberg⁸ in 1951 had isolated the fungus from the soil, and a large number of patients with pulmonary calcifications and positive histoplasmin and negative tuberculin skin tests had been observed. However, the organism has been isolated from the soil,⁹ and the disease recognized in diversified regions of the United States,^{10, 11} so that there is now the belief that histoplasmosis can exist in any age group, in widespread localities, wherein suspicion is alerted and sound mycologic methods are expended.

Diagnosis

Clinical Picture: The clinical expressions of histoplasmosis may be conveniently classified under three general headings: (1) benign pulmonary type; (2) primary muco-cutaneous type; (3) disseminated type.

Benign pulmonary type. There may or may not be symptoms. In the *asymptomatic pulmonary form*, the diagnosis is usually made in retrospect after observing areas of calcification in pulmonary roentgenograms of patients with positive histoplasmin skin tests. The patients may also give positive tuberculin skin tests, but it is now generally agreed that pulmonary calcification is found twice as frequently with associated histoplasmin hypersensitivity as with tuberculin hypersensitivity.^{12, 14} The lesions in the lungs precedent to calcification are infiltrative and difficult to differentiate from similar lesions produced by the tubercle bacillus. The diagnosis can be established by culturing *Histoplasma capsulatum* from the sputum, but this is not always easily accomplished. However, in the event that tubercle bacilli cannot be cultured or demonstrated by direct microscopic technique, histoplasmosis may be suspected. Particularly is this true if

the histoplasmin skin test is strongly positive, and the tuberculin test is negative or only mildly positive.

In the *symptomatic pulmonary form* of histoplasmosis the clinical course of the disease and the roentgenologic findings offer a relatively uniform picture. The onset is sudden, after an incubation period of five to 18 days, with the symptoms of generalized malaise, weakness, vague chest pain, nonproductive cough and fever (102° to 105° F.). There is a paucity of positively pertinent physical findings. During the first few days of illness the roentgenogram of the lungs is unrevealing, but later disseminated and bilateral lesions varying from fine, mottled, granular infiltrations, to soft, miliary nodules are observed. Cavitation occurs rarely. The lesions tend to calcify in three to five years from the onset of the acute illness. Even after the acute phase of the illness has disappeared many of the patients persist for months or even years with symptoms of dyspnea, cough, and abnormal fatigue.

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demics it was believed that the causative organism was *Histoplasma capsulatum*. Then there was the example of a farmer and his two sons in Indiana,¹⁸ who developed histoplasmosis after they had cleaned out a silo that had remained unused for many years. These histories of exposure simply serve to exemplify that histoplasmosis can occur in epidemic proportions, if exposure to dust from soil contaminated with the organism takes place. Nothing more can be concluded.

Primary muco-cutaneous type. Primary lesions involving the skin and mucous membranes occur. In other words, the presence of such lesions is not a part of the picture of disseminated histoplasmosis. The primary cutaneous lesions appear most commonly over the face and neck, and the majority are adjacent to the nares and mouth. The trunk, extremities, and male genitalia may also be affected. The lesions are ulcerative, granulomatous, nodular, papulonecrotic, or they may manifest themselves by abscess formation. A wide variety of disease processes are thereby simulated, namely gumma, primary syphilis, basal cell epithelioma, tuberculosis cutis, granuloma inguinale, blastomycosis, and leishmaniasis. Mucous membrane lesions evolve alone or in association with the cutaneous expressions. The lesions are granulomatous, ulcerative, nodular, or present themselves by producing fissures, hemorrhagic patches or crusts, or perforation of the nasal septum. The tongue, buccal and labial mucosae, gingivae, palate, and larynx may be affected. Syphilis, carcinoma, leukemia, tuberculosis, and leishmaniasis must be ruled out in the differential diagnosis. Regional lymphadenitis usually accompanies muco-cutaneous involvement. Any untreated localized lesion, no matter how simple or benign in appearance, represents a nidus from which dissemination and a subsequent fatal outcome is likely to occur.

Disseminated type. The disseminated and usually fatal type of the disease presents a dissimilar picture from the benign pulmonary and the primary muco-cutaneous types. It has already been emphasized that the primary muco-cutaneous type is very likely to disseminate. On the other hand there are surprisingly few instances of progressive pulmonary histoplasmosis in view of the many cases of primary pulmonary infections. It is tempting to speculate that the form of the organism which is inhaled is less virulent than the form which enters the body through the skin, mucous membranes, and gastro-intestinal tract. Or possibly there are various strains of *Histoplasma capsulatum* that have predilection for different regions of the body, and that these strains command variable degrees of virulence.

The clinical picture is usually that of emaciation, weakness, septic fever, anemia, leukopenia, lymphadenopathy, splenomegalia, and hepatomegalia. Occasionally secondary lesions develop in the skin and mucous membranes that are identical in type and distribution to those occurring in the primary muco-cutaneous form of the disease. Ulcerative lesions may develop in any portion of the gastro-intestinal tract and, depending upon the location of the ulcer or ulcers, symptoms of peptic ulcer or ulcerative enteritis are created. At times erythema and urticaria emerge as evidence of the development of allergy on the part of the host to the invading parasite. Purpura, when it occurs, is either the result of allergy, or thrombocytopenia due in turn to extensive invasion of the hemopoietic system.

Mycology: The fungus in its parasitic phase is a small yeast-like organism ranging in diameter from 2 to 3 microns. These yeast-like bodies resemble closely the Leishman-Donovan bodies of kala azar and invade the mononuclear cells in enormous numbers. Whenever

the diagnosis of histoplasmosis is suspected the mononuclear cells of the circulating blood and the bone marrow should be examined carefully under an oil emersion lens for the intracellular bodies. If there is enlargement of the lymph glands a biopsy should be studied. In sputum the yeast-like bodies are extracellular. Cultures taken from the blood, urine, feces, lymph nodes, or sputum must be placed on both blood agar and Sabouraud's media. On Sabouraud's agar at 30° C. the organism produces ■ white cottony growth. Spores ranging in size from 10 to 25 microns are produced, and from these spores rise finger-like projections 5 microns in length. The growth on blood agar at 37° C. is yeast-like. The gross cultural characteristics of *Histoplasma capsulatum* and *Blastomyces dermatitidis* are accordingly similar.

Skin and Serological Tests: Histoplasmin is a cultural filtrate and contains extracellular antigenic fractions of *Histoplasma capsulatum* produced by growing the organism in a synthetic liquid medium. Histoplasmin is commercially available in concentrated form. For skin testing 1:100 and 1:1,000 dilutions are prepared and the initial test is made by introducing 0.1 ml. of the weaker dilution intradermally. Should the test be negative a similar quantity of the stronger dilution ■ introduced. The test is interpreted exactly as a tuberculin skin test. A negative result to 0.1 ml. of the 1:100 dilution rules out the presence in the past or at the time of testing, histoplasmosis. Cross reactions occurring between histoplasmin and blastomycin or *Blastomyces* vaccine and their evaluation diagnostically have already been discussed in the chapter on blastomycosis.

The diagnostic and prognostic attributes of the precipitin and complement-fixation tests in human histoplasmosis have not as yet been authenticated. In experimentally infected rabbits the precipitin titer reaches a

maximum at a time when the acute symptoms of the infection are at their height, but then in a matter of a few days the titer declines to an indeterminable concentration. The titer of complement-fixing antibodies reaches its peak a few days later than the precipitin titer, falls slightly after a few days, and then remains detectable for many months.^{19, 20} These two serological tests are, therefore, helpful in distinguishing the acute and chronic phases of histoplasmosis in rabbits, but their comparable value in human infections remains at this time unattested.

Treatment

Treatment varies with the clinical type of the disease. In the *benign pulmonary form* of the disease the prognosis is good with non-specific supportive measures of treatment.

In the *primary muco-cutaneous type* the localized lesion, if accessible, should be surgically excised. Sulfadiazine in doses similarly employed in the treatment of actinomycosis and nocardiosis have at times been effective. Iodides, antibiotic drugs, and deep x-ray therapy have been found to be ineffectual.

In the *disseminated type* of the disease only ethyl vanillate, of the many drugs such as promine, actidione, penicillin, streptomycin, aureomycin, chloramphenicol, sulfonamides, iodides, arsphenamine, mercurials, stilbamide and other antimony preparations tried, has given promise of favorably affecting the course of the infection. Ethyl vanillate was developed by I. A. Pearl,^{21, 22} who demonstrated that it had fungicidal properties for some of the fungi which produce spoilage of foodstuffs. The drug was eventually accepted by the Food and Drug Administration for use up to 0.1 per cent in Army foodstuffs. Dr. Amos Christie²³ and his group from the Vanderbilt University School of Medicine developed ethyl vanillate

as a specific therapeutic agent for the treatment of disseminated histoplasmosis. They established its effect in vitro and in vivo; they, with Dr. Ann S. Minot of the Department of Biochemistry of the same university, devised a method of quantitative analysis in the blood, serum and body tissues; they calculated a scale of dosage; they improvised methods of administration; and they enumerated its toxic manifestations and side effects. Before treating a patient with ethyl vanillate the original article by Christie²³ and his associates should be carefully read. Herein, it is only possible to make concise statements which are based entirely on the work of that group.

Ethyl vanillate is administered orally or by gavage. In adults the drug may be given in capsules, but in infants it is preferably administered in a 40 per cent solution of olive oil by gavage. For the infant, the initial dosage should be 0.5 gm./kg./24 hrs., in four to six divided doses. This dose may then be gradually elevated by 0.5 gm every five to six days until an amount of 1.5 gm./kg/24 hrs. is attained, or until the proper blood level is reached. Blood levels of 20 to 30 mg./100 ml. have proven to be therapeutically effective, while levels of 40 mg./100 ml. or more have been associated with undesirable side effects. In calculating the adult dosage it is preferable to relate the quantity to surface area, and on this basis the maximum dose is 5 gm./sq.m. body surface/24 hrs.

Apathy, slight drowsiness and inactivity, which persist throughout the entire period of treatment in variable degrees, disappear soon after ethyl vanillate is discontinued. Hypernea, drug fever, and sudameneous eruptions from excessive perspiration, may occur during treatment but abate following termination of the drug.

The narrow margin between proper therapeutic doses and those which are capable of producing toxic manifes-

tations make it imperative to accompany the cautious administration of the drug with frequent estimations of its concentration in the blood.

The length of time necessary for effective treatment is unknown. Tissues have been rid of culturally demonstrated organisms after eight days of treatment. However, in this disease where there are chronic granulomatous lesions it is advisable, if possible, to maintain therapeutic levels for a maximum of six weeks.

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SPOROTRICHOSIS

ORGANISM: *Sporotrichum Schencki*



LOCALIZED LYMPHATIC TYPE

PURULENT MATERIAL ASPIRATED FROM NODULE

Culture on Sabouraud's Agar

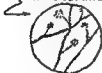
YOUNG CULTURE
(NON PIGMENTED)



OLDER CULTURE
(PIGMENTED - DARK BROWN AND BLACK)



MICROSCOPIC PREPARATION
OF CULTURE



Direct Microscopic Examination



SHOWING PARASITES WITHIN
POLYMERPHONUCLEAR
LEUCOCYTES

ACNEFORM TYPE →
(Especially common in
South America)



Chapter 6

SPOROTRICHOSIS

SPOROTRICHOSIS WAS FIRST discovered in Baltimore by Dr. B. R. Schenck in 1896.¹ Schenck classified the fungus in the genus *Sporotrichum* because the organism produced pear-shaped conidia on minute apiculate processes. In 1900, Hektoen and Perkins² reported the second case and named the organism *Sporothrix Schencki*. These latter investigators apparently believed the names *Sporotrichum* and *Sporothrix* to be synonymous, in as much as the organism they described was morphologically and culturally identical to the fungus isolated by Schenck. Furthermore, they recognized Schenck's priority by establishing *Schencki* as the name of the species. A little later de Beurmann,³ of France, studied the infection and concluded that the fungus producing the disease in France was morphologically and culturally different from the American species. Accordingly, the majority of cases of sporotrichosis in Europe have been and still are reported as being caused by *Sporotrichum Beurmanni*. The supposedly different species, *Schencki* and *Beurmanni*, have been differentiated by the amount of pigment formation, on the degree of spore formation, and on differences in ability to ferment sugars. However, the question of the existence of two species has been set to rest by the demonstration that differences in pigment formation,⁴ spore formation,⁴ and sugar fermentation⁵ are too variable to be used for their separation. It seems most probable, therefore, that although different strains may appear somewhat unlike, there is no valid reason for recognizing any other species than *Sporotrichum Schencki*.

The great majority of patients with this infection have been reported from South America, the United States, and France. The frequency of sporotrichosis in Colombia, South America, should arouse the interest of physicians everywhere. Dr. Manuel Silva,⁶ Professor of Dermatology at the University of Colombia, recalls that there are several thousand victims of sporotrichosis throughout Colombia, and that it is not unusual to see a patient with this infection in his clinic or private offices almost every week.

The fungus lives in a saprophytic stage on vegetation and animals. Many cases have followed wounds of the upper or lower extremities from barberry thorns, straw, or grains. Accidental laboratory infections have occurred, and there is on record a case in which there was direct transmission from human to human. In animals the infection is observed in cats, dogs, rats, horses, donkeys, and wild animals. One of the most spectacular epidemics of mycotic disease ever recorded was the outbreak of sporotrichosis in the gold mines of the Transvaal (Province in Union of South Africa) from 1941 to 1944.⁷ Between 1941 and 1943, 2,441 cases of sporotrichosis developed among the miners at the Ventersport mine, and between 1942 and 1944, 384 cases appeared among workers at the Consolidated Main Reef mine. The source of these infections was traced to a saprophytic growth of the fungus on the wooden mine props. An incidental bit of information arising from this epidemic is that sporotrichosis is a rare disease above ground in the Transvaal where dry conditions prevail. Furthermore, there was a higher incidence of infection in the Ventersport mine which is much cooler and damper than other mines in the area.

Diagnosis

Clinical Picture: The fungus enters the body through wounds to the skin of the upper or lower extremities and

through the gastro-intestinal tract. The great majority of infections occur following trauma to the skin of the hands, but there are rare cases presenting a generalized infection without any primary focus, and in these instances it has been assumed that invasion has taken place through the mucous membranes of the intestinal tract. A few cases have been reported in which there was apparently primary involvement of the lungs. However, in most of the cases of sporotrichosis the lesions will be found in the skin and the subcutaneous tissues.

The clinical picture of a typical case is so striking that, once seen, the disease will always be readily recognized. Extending from the primary lesion, which is usually an ulcer or abscess about the wrist, there will be seen upon the surface of the extremity a line of hard or soft elevated nodules that are neither hot nor tender. Between these nodules there are usually reddened lines that demarcate the course of the lymphatic vessels. If sufficient time has elapsed between the onset of the disease and the time when the patient first presents himself for diagnosis, some of the softer nodules will have developed a draining sinus from which pus can be expressed. It is rare for the infection to spread beyond the regional lymph glands. During this time the patient remains afebrile and is remarkably free from symptoms. It is not uncommon to discover that the patient with sporotrichosis is suffering from some debilitating disease of which he has had no knowledge, but which lowers his resistance to infection sufficiently to allow the fungus to gain a foothold. In this regard there are many cases reported in the literature in which pulmonary tuberculosis has preceded the infection by *Sporotrichum Schenckii*.

It is rare for the infection to disseminate, but when it does the patient becomes acutely ill and cachetic, and death may follow within a period of weeks or months.

In the disseminated cases skin nodules and ulcers appear in any region of the body; the bones and viscera become infected; and the symptoms are those resulting from any chronic granuloma of the organs involved.

There is an *acneform type of the disease* which is a characteristic expression of the infection in Colombia, South America.⁶ The lesions are papular, involving the forehead, eyelids, cheeks, nose, and chin. Some of the papules are hard; others are soft. The latter ordinarily break down, discharging a seropurulent material which dries into a yellowish, bloody crust. The papules may be grouped together about the nose, chin, and upper lip, or they may be diffusely scattered so that most of the face is involved. The clinical picture of a pyoderma is simulated, and because of the location of the lesion a diagnosis of acne vulgaris may be entertained.

Mycology: The diagnosis is established by culturing the organism from a subcutaneous abscess. A high percentage of positive cultures will be obtained if the material to be cultured is aspirated from an abscess that has not yet opened. The character of the growth of *Sporotrichum Schencki* on Sabouraud's agar is distinctive. At first the colony is whitish, shiny, and moist, resembling a bacterial growth, but as the age of the culture increases the whitish color changes to a light tan, then to a coffee brown, and then finally to black. The surface of the colony usually remains shiny, but becomes wrinkled with age. In body tissues and exudates the parasite materializes as a small, single-celled, cigar-shaped organism, which is commonly observed within the polymorphonuclear leucocytes. These structures, the size of larger bacteria, are the only form of the fungus that develops in animal tissues. They are difficult to isolate but are best looked for in smears stained by Gram's technique. The parasites are for the most part, but not always, Gram-negative.

Skin Tests: There is less need of a diagnostic skin test for sporotrichosis than for other systemic fungous infections. This is because the organism is easily cultured and the clinical picture of the infection is invariably typical. A 1:100 dilution of a broth filtrate recovered after two weeks of growth possesses sufficient specific antigenic substance to elicit a positive tuberculin-like skin reaction in a patient infected with the fungus.⁸ Polysaccharides derived from either the fungus mat or the broth filtrate are also effective for skin testing

Treatment

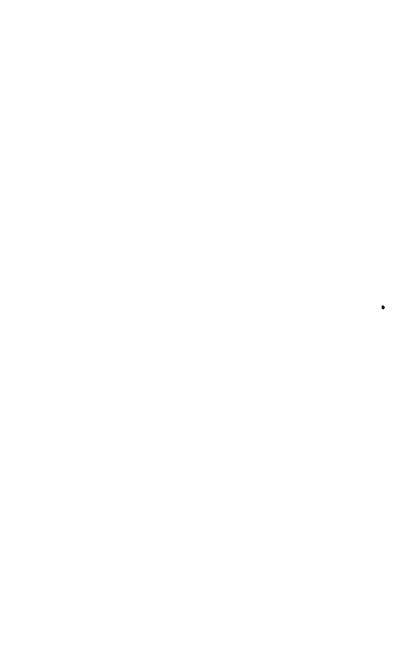
The disease responds dramatically to the administration of large doses of iodides. Ordinarily, it is sufficient to give the official solution of potassium iodide orally. The initial dose is 10 drops, three times daily after meals, and this dosage is then increased by two drops, per dose, per day, to the point of intolerance. The largest dose that can be given without evidence of iodidism must be maintained until one month after recovery; otherwise relapse is a likelihood. There is no objection to the administration of sodium iodide intravenously, and as a matter of fact it is the belief of many physicians in South America that better results are obtained with the intravenous than the oral route of dispensation. Ulcerated lesions of the skin should be painted with tincture of iodine. Nodular lesions that do not show signs of healing after several weeks of systemic iodide therapy should be aspirated and then injected with a 1 per cent solution of iodine. Long standing lesions, vegetating and verrucous, clinically resembling tuberculosis, neither respond to the systemic administration of iodides nor the topical application of strong iodine solution. These lesions should be thoroughly destroyed by electrocoagulation and curetted off. The area is then covered with cotton soaked in iodine solu-

tion, and a dressing applied. Thereafter, healing rapidly takes place leaving a satisfactory cosmetic result.

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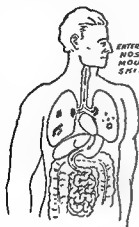
SPOROTRICHOSIS

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CRYPTOCOCCOSIS (TORULOSIS)

ORGANISM

Cryptococcus neoformans

DISTRIBUTION - WORLD-WIDE

PULMONARY TYPE

SPINAL FLUID, SPUTUM,
OR SABOURAUD'S CULTURE

A



B

A Budding cells (no mycelia)
 ■ India ink preparation
 (showing capsules)

CEREBRAL TYPE
(FATAL)

LESIONS

- 1 Meningitis
- 2 Meningo-encephalitis
- 3 May take form of localized tumor

BLOOD STUDIES

Of no value

CEREBROSPINAL FLUID

- 1 Pressure - increased
- 2 Cell count - elevated (lymphocytes usually predominate)
- 3 Glucose - diminished.
- 4 Chlorides - diminished.
- Protein - elevated
- 6 Culture (Sabouraud's) - moist, smooth, cream-colored.

Chapter 7

CRYPTOCOCCOSIS (TORULOSIS)

THE FIRST PROVEN case of cryptococcosis was reported by Busse in 1894¹ and 1895,² and subsequently described by Buschke in 1895.³ Because the Busse-Buschke case was not classically illustrative of cryptococcosis the exact diagnosis remained questionable for years. Fortunately the microorganism isolated from their patient was preserved, and in 1934 after the strain had been studied by Benham,⁴ it was concluded by her that it met all the mycological requirements for classification as *Cryptococcus neoformans* (*Torula histolytica*). The name of the organism responsible for cryptococcosis in man was named *Torula histolytica* by Stoddard and Cutler in 1916,⁵ and it was thereafter that the disease became known as torulosis. There are now grounds for believing that the organism is not a true *Torula* but instead a *Cryptococcus*. The correct name of the fungus is *Cryptococcus neoformans*, the disease it produces is cryptococcosis. Nevertheless, many cases of this infection will be found indexed under torulosis.

✓ The sources of infection of cryptococcosis are obscure. When one is concerned with infective diseases it is natural to suspect that the human disease might be transmitted from one infected subject to another individual. This is not the case for cryptococcosis, because up to this time no such evidence of transmission has been authenticated, and there has been no known contact between human cases. However, it is possible that humans and animals might act as carriers. Virulent strains of *C. neo-*

formans have been isolated from the intestinal tract and skin of healthy individuals, and some animals (cows, horses, oxen, dogs, and cats) have had the disease. Emmons⁴ isolated the organism from soil.

Equally as uncertain as the sources of infection is the portal of entry of the organism and the channels by which it disseminates. Evidence gained by examining reported cases supports strongly the view that the commonest site of entrance to the body tissues is the lungs, and that the organism disseminates from there through the blood stream. It is also suggested that lacerations of the skin and the intestinal tract act as portals for admission into the body, but these sites remain untrustworthy after one carefully appraises data supporting such contentions. The site by which *C. neoformans* gains entry to the lymphatic glands are speculative. When the pulmonary and mediastinal glands are affected it is fair to assume that the organisms reach these glands from the lungs through the lymphatics; moreover from analogy with other diseases, it is possible that involvement of the abdominal glands follows lymphatic spread from the intestinal tract.

Cryptococcosis may be considered to be a world-wide and not a rare disease. Infections have been reported from Europe, India, Australia, Japan, Honduras, South America, South Africa, Canada, and the United States.⁷ There have now been recorded in the medical literature approximately 200 cases of this disease, and the majority of these reports have come from the United States. It becomes evident that with the growing knowledge and interest in mycology that many instances of the disease have been and are being incorrectly diagnosed, and that proven cases are not being recorded.

Diagnosis

Clinical Picture: Herein, the signs and symptoms of

cryptococcosis will be segregated according to the particular tissues affected. Clinical manifestations stem from the central nervous system, the respiratory system, the lymphatic system, the skin, the mucous membranes, and the bones and joints. Ordinarily a combination of these tissues, rather than just one, is invaded by *C. neoformans*, but the evidence of their involvement is usually submerged by the more serious signs of central nervous system disease. Infection of the central nervous system will, therefore, be given priority, and subsequently the less common expressions of the disease will be considered.

Central nervous system. In nearly every case of cerebrospinal cryptococcosis the prevailing signs and symptoms can be attributed to either meningitis or to increased intracranial pressure. As to be expected headache is often the chief presenting complaint. Prodromata, occurring while the organism is proliferating within the subarachnoid space and brain, are frequent. Prodromal symptoms referable to the central nervous system include slight headache, drowsiness, listlessness, temperamental changes, forgetfulness, vagueness, and pain about the body. The prodromata not referable to the central nervous system are evidence of infection in other organs or tissues that preceded the meningitis. Pulmonary disease may be suggested by a cough or hemoptysis, yet there may be simply a lymphadenopathy.

During the course of the mild, prodromal symptoms, or even without previous symptoms, headache begins. Usually the head pain is not severe at first; still it may be so sudden and severe that a diagnosis of subarachnoid hemorrhage is suggested. The head pain is commonly frontal and occipital, but to distribution there is no rule since the pain may be generalized, behind the eyes, or temporal. Vomiting is frequent and often accompanies the headache.

Meningo-encephalitis may or may not be accompanied by fever. Frequently the cranial nerves are involved, and it has been estimated that papilloedema is present in about two-thirds of all cases. The patient may complain of transient dimming or blurring of vision, or a disturbance of accommodation. More severe lesions of the cranial nerves such as external and internal ophthalmoplegia, numbness and pain over the distribution of the trigeminal nerves, weakness of the face, and difficulty in swallowing have been noted.

Focal involvement of the cerebral cortex, suggesting an intracranial tumor, may reveal its presence by generalized or Jacksonian epilepsy, hemiparesis, impairment of sensation of the cortical type, or aphasia.

Clinical signs of spinal cord involvement are rarely observed, even though the spinal subarachnoid space is often found at autopsy to be affected.

Increased cerebral compression, as in all forms of chronic and subacute meningitis, alters the reflexes. The abdominal reflexes may be absent or unequal; the deep tendon reflexes may be hyperactive at first but diminished or absent later, and the plantar reflexes may be absent, or if present they may be of the extensor type, with or without fanning of the toes.

The clinical course of the disease is usually, but not always, one of steady progression to death. The majority of patients die three to four months after the onset of meningitis. Five per cent live for less than a month, and 10 per cent follow a prolonged course, even exceeding a year, or rarely several years. While the disease is running its inevitable end, headache, increasing in severity, continues to remain the predominating symptom of the illness. Death is frequently sudden, perhaps associated with some acute blockage of the cerebrospinal fluid, increased pressure on the brain stem, or cerebral edema.

Although the prognosis is extremely poor it is doubtful that the disease need be invariably fatal. In the human some tissues may resist or apparently destroy the organism; moreover there may be some variability of virulence in different strains of *C. neoformans*.

In the differential diagnosis various types of meningitis must be considered; namely acute pyogenic, tuberculous, syphilitic, and benign lymphocytic. Also space occupying lesions such as tumors, abscesses, gummata, tuberculomata, and, infrequently, hydatid cysts, require elimination.

Respiratory system. Pulmonary involvement is, in frequency, second only to that of the meninges and brain. Cryptococcosis may rarely remain confined to the lungs, but a few reports in the literature attest to this isolation. It is conceivable that pulmonary cryptococcosis might occur without being diagnosed, because few signs or symptoms accompany lung involvement and the organism is rarely looked for in the sputum unless it has previously been demonstrated in the cerebrospinal fluid. The majority of cases of cryptococcosis of the lungs occur in patients who have co-existing lesions in other tissues, especially the central nervous system.

It is common, though not unvarying, for pulmonary cryptococcosis to be accompanied by only meager local and constitutional signs and symptoms. Symptoms when present are those of a cough with some expectoration; also hemoptysis may occur. Occasionally pleural pain may appear, or a small effusion be present in the pleural cavity. Rarely does the infection produce a disease of clinical severity. Physical signs, if present, are those of a bronchitis or consolidation.

A roentgenogram of the lungs is helpful and important in making a diagnosis. Because the pulmonary lesions may assume one of several forms, the shadows cast by

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common and so striking that students of the former disease have stipulated the belief that chronic cryptococcosis may result occasionally in true Hodgkin's disease.

Skin and Mucous Membranes. Lesions in the skin occur in about 5 per cent of the cases. Usually the cutaneous involvement is secondary and not primary. The manifestation, a granuloma which usually breaks down to form an ulcer, can not be identified with cryptococcosis unless the cryptococcus has been identified by culture or in section of the tissue, or unless there is evidence of involvement of other tissues of the body as the meninges or lungs, with recovery of the organism from the cerebrospinal fluid or sputum. However, if the etiology remains in doubt other systemic diseases in which granulomatous lesions of the skin and subcutaneous tissues occur must be considered. These conditions are tuberculosis, syphilis, Boeck's sarcoid, and such mycotic infections as blastomycosis, coccidioidomycosis, and sporotrichosis.

Infections of the mucous membranes are very uncommon. Reports of oral ulcerations and orbital and paranasal sinus invasions have appeared in the literature.

Bones and Joints. Bone involvement occurs in about one out of 10 patients. Although the infection may be localized and remain isolated, it is usually part of a generalized infection. Under the latter circumstances the lesions are frequently multiple and widely disseminated, tending to involve bony prominences and to be osteolytic, exciting very little bone reaction. The roentgenological picture is more reminiscent of blastomycosis and coccidioidomycosis than actinomycosis. A bony lesion that is isolated and not a part of a generalized infection may spontaneously heal.

Laboratory Picture: The cerebrospinal fluid may be clear, colorless, yellow, or turbid. The intraspinal pressure is usually over 200 mm. of water. The cell counts of

the lesions are variable and depend upon the type of pathological changes present. When there is an abscess a fairly dense shadow will be cast upon the film which suggests a tumor, pyogenic abscess, or hydatid cyst. In addition to or unassociated with the cryptococcus abscess there may be smaller, granulomatous areas, and fibrosis in close proximity to the bronchi, which produce together on the x-ray film linear markings surrounded by woolly shadows. This picture, therefore, is similar to that observed in pulmonary moniliasis. The pathological changes and, therefore, the x-ray findings, commonly occur at the base or mid-zone region of the lungs, but they need not and do not always appear at these sites. The lesions just described are produced by collections of *C. neoformans*, and may be of any size

The only exacting proof of pulmonary cryptococcosis is the finding of the organism in the sputum. Fortunately the Ziehl-Neelsen stain is excellent for detecting *C. neoformans* as well as the tubercle bacillus. An India ink preparation of sputum shows up the capsules of the organism brilliantly, and thus aids in their identification.

Pulmonary cryptococcosis must be differentiated from other chronic lung diseases such as, tuberculosis, unresolved pneumonia, pyogenic abscess, bronchitis, bronchiectasis, fibrosis, primary and secondary carcinoma, Boeck's sarcoid, hydatid cyst, and other mycotic infections.

Lymphatic System. Enlargement of the lymphatic glands are observed clinically or at autopsy in about one out of six patients with cryptococcosis. The lymphadenopathy may be the result of the fungus infection, but quite often no relationship can be established, and it eventually develops that the cryptococcus infection is coincident with some form of lymphoblastoma. The association of cryptococcosis and Hodgkin's disease has been so

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on a reddish color when the cells are stained by Gram's technique.

Skin and Serological Tests: The antibody response in cryptococcosis is poor; consequently precipitin, agglutination, and complement-fixation tests are of no importance in the diagnosis. Investigation of the diagnostic significance of skin tests has been so meager that comments in this regard are pointless.

Treatment

In this disease where spontaneous remissions are common it is nearly impossible to assess the value of any therapeutic remedy. Remissions may be so prolonged that patients are able to resume their occupations. Exacerbations inevitably occur with a fatal termination. It is true, however, that localized infections may heal spontaneously. The unfavorable prognosis of cryptococcosis is undoubtedly due to poor antibody response, the protective effect on the virulent cryptococci of their thick capsular and extra-capsular coating, and the inefficient phagocytic reactions of the host cells.

It is impossible to enumerate a specific method of treatment; none exists. It is not inferred that a hopeless attitude be assumed. When presented with a case of cryptococcosis, chemotherapeutic tests on mice with all likely promising drugs should be performed. There is always the possibility that the specific strain of *C. neoformans* isolated will be susceptible to one of the sulfonamides, to one of the antibiotics, to actidione, to propamidine, or to some other drug that has not been discovered or synthesized at the time of this writing.

Immunization with a vaccine of *C. neoformans* prepared and administered as *Blastomyces* vaccine should be tried and continued during the entire course of the disease. If possible a weakly encapsulated strain of the or-

the cerebrospinal fluid are extremely variable (10-500/c.mm.). Lymphocytes usually predominate. The total protein content is often raised above 40 mg. per cent. The chloride content is frequently lowered to 650 mg. per cent; the glucose, which is low, may range between 7 to 25 mg. per cent.

A diagnosis is established by demonstrating the encapsulated budding yeast cells in the centrifuged spinal fluid sediment. The cryptococcus cells are difficult to identify in wet preparations, and are easily confused with lymphocytes and red blood cells. The yeast cells are more readily found if an amount of the spinal fluid sediment is diluted with an equal quantity of a 0.2 per cent solution of methyl violet in 1 per cent aqueous acetic acid. After the mixture has stood for a few minutes it is examined in a counting chamber. The capsule of the cryptococcus in this preparation remains unstained, and the organism is distinctly visible in the blue background. The cell body of the cryptococcus stains less deeply and less uniformly than the nuclei of the lymphocytes.

The cryptococcus is very difficult to recognize by the direct microscopic examination of wet sputum. However, the encapsulated organisms are readily discovered with the low-power microscope lens if the sputum is stained by the Ziehl-Neelsen method.

The hemogram is not helpful in the diagnosis. The total white blood cell count is usually slightly elevated with an associated increase in the percentage of polymorphonuclear neutrophils.

Mycology: On Sabouraud's medium at 30° C. the organism grows slowly. At first the growth is moist, smooth, and cream colored. As the culture ages the color changes to yellow and then to brown. A portion of the culture examined microscopically and in an India ink preparation reveals best the wide typical capsules. This capsule takes

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ganism should be employed in the vaccine, since there is evidence that vaccines prepared from such strains are more immunogenic than vaccines prepared from the strongly encapsulated ones.⁸

Cryptococcus neoformans enjoys an acid medium and fails to survive at temperatures of 105° to 107° F., for seven and six days respectively. Accordingly, alkalization and hyperthermia have been suggested as possible methods of treatment. Attempts thus far with alkalization have met with failure; hyperpyrexia has not been adequately tried.

Localized infections of the subcutaneous tissues are best treated by opening and drainage, after which they may heal. The surgical measures should be supplemented by local x-ray irradiation.

Pulmonary lesions that are isolated and not part of a generalized infection may heal. However, since they are very likely to disseminate the early surgical excision of the circumscribed lesion is advisable.⁹

General measures of treatment are those common to all serious diseases. The headache of the meningitis may be relieved by common analgesics, but frequently only opiates are effective. The withdrawal of cerebrospinal fluid relieves head pain temporarily.

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Chapter 8

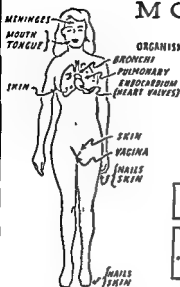
MONILIASIS

OF THE MANY SPECIES included in the genus *Candida* (*albicans*, *tropicalis*, *pseudotropicalis*, *Krusei*, *parakrusei*, *stellatoidea*, and *Guilliermondi*) only one, *albicans*, is commonly pathogenic for man. The clinical manifestations of infection produced by this microorganism vary greatly, and are dependent upon the region of the body involved. (Moniliasis is the term which designates an acute or a chronic infection, produced by the *Candida* organism, occurring in the mouth, vagina, skin, nails, bronchi, lungs and, infrequently, in the endocardium and meninges.) It is important to bring under one's notice that mycologists have replaced the familiar generic term, *Monilia*, with the name *Candida*. The name of the fungus, *Monilia albicans*, therefore, becomes *Candida albicans*. Notwithstanding the change in the name of the genus, the term moniliasis, because of its common usage in the medical literature, has been retained in spite of suggestions that candidosis or candidiasis might be more appropriate.

With the advent of the antibiotic era a host of complex situations have emerged which at first were looked upon as collateral findings secondary to curing the primary infections, but which now are assuming great importance in their own right. The situations which are appurtenant to this section are the unfavorable side-reactions that accompany the administration of the wide-spectrum antibiotics. The great majority of these side-effects follow mucous membrane irritation and emerge as

MONILIASIS

ORGANISM: *Candida albicans*



DISTRIBUTION - WORLD WIDE

SKIN TEST

• Of no value

SEROLOGY

Agglutinins } May or may not
Precipitins } be present.

SPUTUM OR OTHER MATERIAL

DIRECT MICROSCOPIC



ON ROSIN-
METHYLENE BLUE
PLATE,
MICROSCOPIC
APPEARANCE



MICROSCOPIC
APPEARANCE



CULTURE - GELATIN OR CORNMEAL AGAR STAB



MICROSCOPIC
APPEARANCE



GLUCOSE (ACID & GAS) MALTOSE (ACID & GAS) SUCROSE (ACID)

Chapter 8

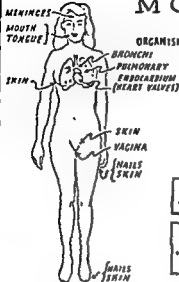
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CULTURE - GELATIN OR CORNMEAL AGAR STAB

MICROSCOPIC
APPEARANCE



GLUCOSE (ACID & GAS) MALTOSE (ACID & GAS) SUCROSE (ACID)

Diagnosis

Clinical Picture: *Infection of the mucous membranes of the mouth* (thrush) is the commonest expression of moniliasis. The typical lesion is a whitish membranous plaque which is easily scraped from the underlying inflamed mucous membrane. The plaque represents a large colony of the fungus (budding cells and filaments) in essentially pure form, and comparable in gross and microscopic appearance to its growth on Sabouraud's medium. Thrush occurs more frequently in children than in adults, and in the former it is generally believed that infection occurs during birth from a mother with a vaginal infection. In adults, thrush may occur associated with some debilitating disease.

Infection of the mucous membranes of the vagina, with or without concomitant vulval involvement, is nearly as common an expression of moniliasis as thrush. Here the lesion is identical to that described for thrush. It must be strongly argued that the mere finding of budding cells and filaments in direct smears from the vagina cannot be considered diagnostic of moniliasis; these may be found in perfectly normal individuals who have or have not received antibiotics. Only the demonstration of a solid mass of budding cells and filaments within a grossly detachable membrane makes for a valid diagnosis.

Infection of the skin ordinarily follows autoinoculation of *C. albicans* from the mouth, vagina, or intestinal tract. Moisture is a prerequisite for cutaneous involvement. Intertriginous lesions of the fingers follow maceration of the skin from frequent and continued immersion in water. Housewives, bartenders, waiters, chefs, bakers, and fruit canners are prone to develop this type of infection. Intertrigo of the axillae, intergluteal folds, inframammary folds, groin, and webs of feet may develop in obese individuals and those that perspire excessively. Infection

stomatitis, glossitis, black hairy tongue, perlèche, diarrhea, anal and vulval pruritus, and genitocrural lesions. Because *C. albicans* has been isolated frequently and easily from patients exhibiting these reactions, it has been assumed that such are expressions of moniliasis. This diagnosis must not be made without deliberation, because the isolation of *C. albicans* alone is insufficient evidence for such a conclusion.

Candida species are inhabitants of the normal mouth, intestinal tract, and vagina, and may be cultured from these sites in 35 to 40 per cent of normal persons.¹ The organism has never been isolated from the skin except where there is an associated cutaneous disease. The organism is also found frequently in the sputa of patients with nonmycotic bronchial and pulmonary disease, and in the stools of patients with diarrhea unrelated to fungous infection. Therefore, in addition to the isolation of *Candida*, it is imperative for the clinical picture to be that produced by the organism before a diagnosis of moniliasis is entertained. Kligman,² in emphasizing the difficulties of this diagnostic problem, has pointed out that the local pathology observed and often ascribed to moniliasis may be due to other conditions; for instance, vitamin deficiency, allergic reactions, other bacterial and viral infections, or other irritations overlayed with moniliasis. Quantitative studies have demonstrated that the wide-spectrum antibiotics fail to enhance the growth of *C. albicans* in vitro,³ and exacerbate moniliasis in experimentally infected animals.² Taking one thing with another it is contended that, although *C. albicans* is found in abundance in the mouths and gastrointestinal tracts of persons receiving wide-spectrum antibiotics and is isolated in the presence of some unfavorable side-reactions resulting from these drugs, the diagnosis of moniliasis in a great majority of these individuals is unfounded.

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also occurs rather commonly in patients with diabetes mellitus, probably because the altered carbohydrate metabolism may favor the growth of the organism. The cutaneous lesions are characterized by reddened, weeping areas with well-defined vesicopustular or papulosquamous borders. The demonstration of budding cells and filaments in direct smears taken from clinically characteristic skin lesions meets all the requirements for an exacting diagnosis of cutaneous moniliasis. However, it must not be forgotten that *C. albicans* may become established in skin lesions that have been treated topically with wide-spectrum antibiotic ointments. This is most likely to occur when these ointments have been applied to chronic lesions for a week or more. Lesions that are prone to heal quickly are usually not invaded by *C. albicans*. Kligman² and Livingood,⁴ who have observed the invasion of *C. albicans* in chronic skin lesions, have not noticed the development of classical cutaneous moniliasis in these lesions, nor have they noticed thus far that the presence of *C. albicans* has inhibited the gradual healing process of the primary lesions.

Infection of the nails (onychia and paronychia) is manifested by swelling at the nail bed, which may be painful and resemble a bacterial infection, and by thickening and transverse grooving of the nails.

Bronchopulmonary moniliasis is the term employed to designate that type of *Candida* infection of the lungs in which the disease process is limited to the bronchial tree. This type of infection, which is not at all uncommon, is manifested clinically by the signs and symptoms of an ordinary bronchitis. The temperature may be normal or only slightly elevated, and the health of the patient is not seriously affected. Roentgenograms of the lungs reveal slight to moderate peribronchial thickening. The infection may disappear spontaneously or become chronic and

mimic the symptoms of a chronic bronchitis of bacterial origin.

Pulmonary moniliasis is the term reserved for infections of the parenchyma of the lungs. While the parenchymal is not so common as the bronchial infection, it is in turn a more serious one. Pulmonary moniliasis, with symptoms of cough, fever, dyspnea, chest pain, hemoptysis and night sweats, may resemble military tuberculosis. There may be signs of pleural thickening. Areas of consolidation resembling a bronchopneumonia may be scattered throughout two or more lobes, and infrequently there may be lobar consolidation.

The diagnosis of bronchopulmonary and pulmonary moniliasis is fraught with difficulties. Isolation of the organism, particularly if the patient has received antibiotics, is not conclusive. The organism frequently establishes itself in the bronchial mucous membranes as a secondary invader. A diagnosis must be made indirectly by excluding all other conditions, infections and neoplasms, that might affect the bronchial and parenchymal tissue, and by demonstrating repeatedly the organism in the sputum. Actually there are no indisputable criteria for establishing the diagnosis short of the impractical procedure of lung biopsy.

Systemic infection usually follows chronic, refractory skin and oral mucous membrane lesions, and uncommonly such infections have been followed by invasions of the meninges. Although *C. albicans* is usually considered to be the only pathogenic member of the *Candida* genus, mycotic endocarditis due to *C. parakrusei* has occurred in dope addicts. *C. albicans* and *C. Guilliermondii* have also been the causes of endocarditis.

Clinical manifestations of anaphylactic hypersensitivity may develop during the course of a *C. albicans* infection. *Bronchial asthma* was reported by the author

to have followed a bronchial infection.⁵ The asthmatic symptoms completely disappeared with the alleviation of the infection. The author has also observed, but not reported, the development of *urticaria* in a patient with cutaneous moniliasis. The *urticaria* disappeared as soon as the infection had been cured. The author likewise has observed in the past year the development of a typical *allergic eczema* in a two year old child one month following the administration of aureomycin. *Candida albicans* was isolated from the stools. The child was treated only with the official solution of potassium iodide, which was given throughout the entire period of observation, and two courses of methylosaniline chloride (gentian violet), 0.032 gms. by mouth, twice daily, for six days, at monthly intervals. *Candida albicans* disappeared from the stools after four months, and the skin was normal after 5½ months.

Eczematoid dermatitis of the face and certain cases of *miliaria* are thought to be allergic reactions to *Candida* infections. In the instance of *miliaria* and facial dermatitis the focus of infection has been considered to be intestinal. Vesicular lesions on the hands, referred to as *moniliids* and similar in appearance to dermatophytids, are the result of allergic reactions to infections occurring elsewhere in the body.

Skin and Serological Tests: Agglutinins and precipitins are not usually present in the sera of patients with mucous membrane and cutaneous moniliasis, but are present occasionally in patients with severe forms of systemic infections. Even the latter observations are clouded diagnostic criteria because many normal individuals have agglutinins in their sera for *C. albicans*. Skin tests are of no value because of the high percentage of positive reactions in patients without active infection

Mycology: To establish the diagnosis of moniliasis,

budding cells and filaments must be observed by direct examination of plaques, sputa, or exudates, and the organism isolated in pure culture form on Sabouraud's agar. On Sabouraud's medium the organism grows as a yeast, but when stab cultures are made in gelatin or corn meal agar the mycelial form of the fungus is reproduced. To make certain that the organism isolated is the pathogenic species of *Candida*, it should be tested for fermentation reactions. *Candida albicans* will form acid and gas in glucose, acid and gas in maltose, but only acid in sucrose media. Recently Weld⁶ has described a technique for the rapid identification of *C. albicans*. The organism grown on modified eosin-methylene blue medium in an atmosphere of 10 per cent carbon dioxide can be easily identified after a period of 18 hours from the other species of *Candida*. The colonies of *C. albicans* take on a "spidery" or "feathery" type of appearance. All of the other species of *Candida*, with the exception of *C. stellatoidea*, fail to develop mycelia on this medium. The growth of *C. stellatoidea* is so different from that of *C. albicans* that they cannot be confused.

Treatment

Methylrosaniline Chloride N F (gentian violet), in a 1:100 solution, may be used as a paint twice daily in the treatment of oral and vaginal moniliasis. Methylrosaniline Chloride Jelly, N F., which contains 1 per cent of the dye in a water-soluble jelly, is suitable for the treatment of vaginal infections. Sodium caprylate is both fungistatic and fungicidal for *C. albicans*^{7,8}. Sodium Caprylate, N.N.R. may be employed in concentrations of 10 to 20 per cent in solution for the treatment of oral moniliasis, and the Caprylic Compound, N.N. II (Naprylate) may be used in powder, jelly, or suppository form for the management of vaginitis.⁹ Regardless of the preparation em-

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Mycology: To establish the diagnosis of moniliasis,

dides, gentian violet, or nystatin (fungicidin). Iodides are prescribed in the form of the official solution of potassium iodide in the manner previously described for blastomycosis. Gentian violet, in doses of 0.032 gms., is given twice daily for ten days. Such a course may be repeated at monthly intervals. Nystatin is administered in doses of 500,000 units three times daily for four days. The course may be repeated, as necessary, until the stool cultures are negative for *C. albicans*. Any combination of the three medications may be employed if one drug administered singly has proven ineffective.

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ployed, it is advisable, when possible, to remove the membranous plaques before applying medication.

Intertriginous areas (hands or feet) should be treated with potassium permanganate soaks (1:3,000), three times daily. Following each 20-minute period of soaking, Caprylic Compound, N.N.R. ointment, or a 1:100 solution of Methylrosaniline Chloride, N.F., prepared in 10 per cent alcohol should be applied. If onychia and paronychia fail to respond to the above measures fractional x-ray therapy may prove successful.

Bronchopulmonary moniliasis is best treated with potassium iodide by mouth and sodium caprylate by aerosol.⁶ The official solution of potassium iodide should be given in as large a dose as can be tolerated by the patient; the scheme for treatment is identical to that already enumerated in the chapter on blastomycosis. One milliliter of the 10 per cent solution of Sodium Caprylate, N.N.R. should be given by aerosol several times daily. Best results are obtained if a total daily dose of 1 gram is achieved.

Pulmonary moniliasis is treated in a manner identical to that of bronchopulmonary moniliasis. Gentian violet should be given intravenously if the patient is not doing well on iodide and caprylate therapy. The dosage is 5 mg /kg., and may be repeated daily or every other day for three to seven doses.

It is usually advisable before administering potassium iodide to give the patient three to four weeks of specific desensitization treatment with *C. albicans* vaccine. The vaccine is prepared, and the dilutions and dosages are calculated, by the same techniques described for *Blastomyces* vaccine in the chapter on blastomycosis. The prolonged use of a *C. albicans* vaccine in the management of patients with chronic infections is recommended.

Intestinal moniliasis may be treated orally with io-

nonspecific findings of diffuse peribronchial thickening are observed in pulmonary roentgenograms.

Parenchymal invasion of the lungs produces signs and symptoms suggestive of pulmonary tuberculosis. The temperature, pulse, and white blood cell count are elevated. The sputum is mucopurulent and may or may not contain blood. The physical findings are not specific, but may lead one to suspect tuberculosis. Pulmonary roentgenograms reveal patches of infiltration with or without cavity formation.

Mycology: Microscopic examination of infected material reveals oblong or rectangular cells, 4 to 8 microns, with rounded ends, and/or large spherical cells, 4 to 10 microns in diameter.

At room temperature on Sabouraud's medium the organism grows rapidly and forms a white to cream colored colony with a dry, mealy surface. Microscopically, the hyphae are seen to segment into rectangular arthrospores, which vary in size and roundness of their ends. There are also many spherical cells which are segmented from the hyphae but fail to remain rectangular. The rectangular cells ordinarily germinate by a germ tube from one corner. This is a very characteristic finding in cultures of *Geotrichum*.

Treatment

One of the important reasons for recognizing geotrichosis as a specific entity is to avoid confusing this fungus disease with North American blastomycosis. This is because the prognosis is usually good with geotrichosis and poor with blastomycosis.

Oral infections respond favorably to topical gentian violet therapy. The scheme of treatment is identical to that used in the management of thrush due to *C. albicans* (see chapter on moniliasis)

Chapter 9

GEOTRICHOSIS

THERE HAS NEVER been a careful study of the saprophytic and pathogenic species of the genus *Geotrichum*. It is only possible to state, therefore, that geotrichosis is a fungous infection due to one or more species of *Geotrichum*. The organism is capable of producing lesions in the mouth, intestinal tract, bronchi, and lungs.

Geotrichosis, like moniliasis, is probably endogenous in origin. The organism is frequently isolated from the mouths and intestinal tracts of normal individuals.

Diagnosis

Clinical Picture: The *oral lesions* are indistinguishable clinically from thrush. A differentiation between geotrichosis and moniliasis is made only by direct microscopic examination of the white patches which are easily removed from the mucous membranes. In geotrichosis the characteristic rectangular spores are readily discernible.

Intestinal invasion produces symptoms of colitis, with or without blood in the stools. The diagnosis of geotrichosis must not be entertained until the organisms are consistently demonstrated in the stools and all other possible causes for the symptoms have been excluded.

Bronchitis is probably the most frequently recognized manifestation of geotrichosis. The symptoms are identical to those of chronic bronchitis of bacterial origin. The sputum is often gelatinous, the pulse and temperature are rarely elevated, and the general health is good. The physical examination usually reveals medium and coarse rales which are noticeable especially at the lung bases. The

Intestinal geotrichosis is treated in a manner identical to that employed for intestinal moniliasis (see chapter on moniliasis).

Bronchitis responds readily to oral iodide therapy administered as outlined in the chapter on blastomycosis.

The pulmonary form of the disease should likewise be treated with iodides but such therapy should not be instituted until tuberculosis has been excluded in the differential diagnosis. If the infection does not respond to iodide therapy an autogenous vaccine, prepared and administered in the same manner as *Blastomyces* vaccine, should be tried. Also in the event that iodides are ineffective, neomycin should be prescribed. Neomycin has proven effective in the treatment of septicemia¹ and urinary tract infections due to *Geotrichum*.² It must be emphasized that neomycin, if administered for any length of time, is a toxic antibiotic which causes deafness as well as renal damage.

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GEOTRICHOSIS

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Chapter 10

CHROMOBLASTOMYCOSIS

CHROMOBLASTOMYCOSIS was first reported on by Lane¹ in 1915. In the same year Medlar² grew the causative organism and adopted as a name for the fungus, *Phialophora verrucosa*. Actually Pedroso³ had studied a case of chromoblastomycosis in Brazil as early as 1911, but it was not until 1920 that his report appeared in the literature. Pedroso believed that the organism isolated from his patient was the same as that recovered from Lane's patient; however this was not the case. Brumpt⁴ in 1922 studied the organism and named the South American strain *Hormodendrum Pedrosoi*. Thereafter, there remained some doubt as to whether strains similar to the South American organism should be included in the genus *Hormodendrum*. At the present time there is a tendency to classify all such organisms in the genus *Phialophora*. There are three species of *Phialophora* that are recognized as causes of chromoblastomycosis, namely, *P. verrucosa*, *P. Pedrosoi*, and *P. compactum*.

The disease, world-wide in distribution, affects the skin of the exposed parts of the body. It occurs most frequently in the tropics among barefooted, agricultural laborers, and others having close contact with the soil.

The name of the disease, chromoblastomycosis, was selected because the fungus cells in the lesions were of a dark color, and because the pathological process resembled North American blastomycosis.

Diagnosis

Clinical Picture: The disease is confined to the skin,

CHROMOBLASTOMYCOSIS

ORGANISM ■

Phialophora verrucosa
Phialophora Pedrosoi
Phialophora compactum



DISTRIBUTION - WORLD WIDE



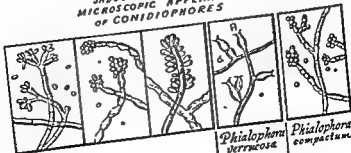
DIRECT MICROSCOPIC EXAMINATION

⇒ PUS ⇒



DARK BROWN SEPTATE BODIES

CULTURE ON
 SABOURAUD'S AGAR;
 MICROSCOPIC APPEARANCE
 OF CONIDIOPHORES

*Phialophora Pedrosoi**Phialophora verrucosa**Phialophora compactum*

tical diagnostic aids. The diagnosis is made readily from the clinical picture and the recovery of the organism from the pathological lesion.

Treatment

The disease is slowly progressive but never fatal. If the patient is seen early in the course of the disease the lesion or lesions should be removed by surgical excision, cauterization, or electrocoagulation. If the infection has progressed so that removal is impossible, then local x-ray therapy combined with the oral administration of large doses of the official solution of potassium iodide or the intravenous administration of sodium iodide should be recommended.

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and for the most part the lesions are unilateral and occur on the lower extremities. At first there are warty growths which travel slowly as satellite lesions along the lymphatics. Over a period of months the lesions enlarge to become pedunculated, cauliflower-like excrescences, which may or may not ulcerate. Elephantiasis of the affected limb, when it occurs, is the result of marked fibrosis and lymph stasis. Regional lymphadenopathy and constitutional symptoms occur only if there is secondary bacterial infection present in the primary mycotic lesion. Pain and pruritus are uncommon.

Mycology: The diagnosis is established by demonstrating the brownish, thick-walled, septate cells in pus removed from lesions, or by growing one of the three species of *Phialophora* in culture form.

Phialophora Pedrosoi grows slowly on Sabouraud's agar as a dark green, brown, or black velvety colony. Microscopically the fungus varies greatly in its method of conidia formation. Three different types of sporulation are recognized: conidia in branching chain formation from conidiophores; conidia surrounding the swollen, knotted, club-shaped, terminal ends of hyphae; and conidia produced semiendogenously from flask-shaped conidiophores.

Phialophora compactum grows slowly on Sabouraud's agar and produces a heaped, dark green to black colony with tufts of coarse aerial mycelium. Microscopically this species is distinguished from *P. Pedrosoi* by its chains of spherical conidia arranged in compact sporulating heads.

Phialophora verrucosa, on Sabouraud's agar, produces a dark brown to black colony with gray aerial mycelium. Microscopically there are flask-shaped conidiophores which arise terminally or laterally from the hyphae. Conidia are produced at the tip of the conidiophores.

Serological and Skin Tests: These tests are not prac-

tical diagnostic aids. The diagnosis is made readily from the clinical picture and the recovery of the organism from the pathological lesion.

Treatment

The disease is slowly progressive but never fatal. If the patient is seen early in the course of the disease the lesion or lesions should be removed by surgical excision, cauterization, or electrocoagulation. If the infection has progressed so that removal is impossible, then local x-ray therapy combined with the oral administration of large doses of the official solution of potassium iodide or the intravenous administration of sodium iodide should be recommended.

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Serological and Skin Tests: These tests are not prac-

Chapter II

SOUTH AMERICAN BLASTOMYCOSIS

A COMMONLY FATAL DISEASE occurring in Brazil, characterized by ulcerative lesions in the mouth with enlargement of the regional lymph nodes, was reported upon first by Lutz¹ in 1903. At first the causative organism was thought to be related to *Coccidioides immitis*, but later when the differences of the two were recognized the Brazilian fungus became known as *Paracoccidioides brasiliensis*. It was not until 1942, after Conant and Howell² had studied the organism and demonstrated its similarities to *Blastomyces dermatitidis*, that the fungus was transferred to the genus *Blastomyces*. The current accepted name is *Blastomyces brasiliensis*.

The disease is confined to South America and occurs principally in Brazil. The greatest number of cases from Brazil have been reported as coming from the state of São Paulo. Isolated cases have appeared in Venezuela, Peru, Argentina, and Paraguay.

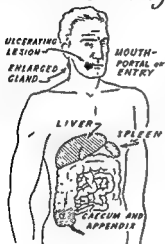
The habitat of the fungus remains unknown. There have been no reports of spontaneous infection in animals. There is some evidence that the disease may be transferred from man to man.

Diagnosis

Clinical Picture: The mouth, which is apparently the portal of entry, is commonly the site of an ulcerating lesion, that spreads peripherally causing rapid and extensive tissue destruction. Eventually the lesions in the mouth spread to the adjacent skin of the lips and nose where they form crusted or nodular lesions resembling

SOUTH AMERICAN BLASTOMYCOSIS

ORGANISM *Blastomyces brasiliense*



SEROLOGY

Complement-fixation :

- (1) Positive during disease.
- (2) Negative after recovery

PUS FROM LESION

CULTURE

On blood agar at 37°
produces yeast-like colony
MICROSCOPIC APPEARANCE:



DIRECT MICROSCOPIC

May show character-
istic cells, with
multiple buds, as
in early culture.

which several strains of *B. brasiliensis* have been grown, and a vaccine prepared from the yeast phase of the organism have been used for skin testing. The tests are interpreted as the tuberculin skin test

Treatment

The disease usually responds favorably to sulfonamide therapy.^{3, 4, 5} Sulfadiazine or sulfamerazine, in doses of 1 gm. every six hours, should be administered until there is evidence that the infection is subsiding. The dose may then be reduced to 2 or 3 gms. every 24 hours, and maintained at this level for several weeks after recovery. Iodides and other drugs commonly employed in the management of mycotic infections are ineffective.

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North American blastomycosis. Finally the lymph glands of the neck become enlarged and it is not long, if the patient remains untreated, until the glands break down and drain through skin penetrating sinuses. Occasionally the cervical lymph glands become infected without preceding demonstrable oral lesions.

Although the primary lesions are commonest in the mucous membranes of the mouth, they also may develop in the mucous membranes of the gastro-intestinal tract. In the visceral type of infection, ulcers form in the region of the cecum and appendix and enlarge as they do in the mouth. The organisms spread via the lymphatics and blood stream with the final establishment of a massive visceral infection. The lungs rarely are affected.

Mycology: To establish the diagnosis, *B. brasiliensis* must be demonstrated in the lesions or a positive culture obtained. The organisms appear in tissues or giant cells as large, round (10 to 60 microns) cells with small or large peripheral buds. The multiple budding is characteristic of *B. brasiliensis*.

On blood agar at 37° C., a smooth, yeast-like colony is produced which is made up of numerous round, multiple-budding cells identical to those observed in the tissues. On Sabouraud's medium at 30° C., the organism produces a compact colony, which at first is smooth, but later is roughened by short aerial mycelium that change in color, with age, from white to light brown.

Serological and Skin Tests: The titer of the complement-fixation test rises during spread and dissemination of the infection, and declines as the disease is successfully treated. The test becomes negative soon after the disease has been cured. For prognostic assistance, the concentration of complement-fixating antibodies should be followed during the course of the disease.

Paracoccidioidin, a filtrate of Sabouraud's broth in

foliation of the epithelium. The accumulation of the epithelial debris eventually causes an obstruction in the canal, accordingly there is an impairment of hearing. Quite often there follows an associated bacterial infection with the production of suppuration and pain. If the infection becomes chronic, eczematoid changes develop in the epithelium and this process extends itself to the external ear and the adjacent skin of the neck. The clinical picture of external ear disease may be produced also by species of *Mucor*, *Penicillium*, *Rhizopus*, or *Candida*.

Primary pulmonary infection is rare, and the diagnosis is usually made following a postmortem examination ^{4, 5, 6}. The symptoms and signs may be those of pulmonary tuberculosis, or other mycotic infections that involve the lungs. Here again there is nothing typical of an *Aspergillus* infection.

It is not uncommon to isolate *Aspergilli* from the sputum of patients with chronic bronchitis and infective bronchial asthma, but it is virtually impossible to prove that the fungus has anything to do with the etiology of the infection or the hypersensitive state.

Isolated examples of *paranasal sinusitis*, *vaginitis*, *meningitis*, and *involvement of vertebrae and ribs* have been recorded.

Mycology: Direct microscopic examination of sputum reveals broken fragments of hyphae with many small (2 to 3 microns), round, dark green conidia.

On Sabouraud's medium at 30° C., the organism grows rapidly, appearing first as a white cottony growth. With the production of conidia the color of the colony rapidly turns to a green or dark green. Microscopic preparations should be made by carefully placing a small portion of the aerial growth in lactophenol cotton blue and covering with a cover slip. The characteristic swollen conidiophore, bearing the sterigmata and then the chains of conidia,

Chapter 12

ASPERGILLOSIS

SPECIES OF *Aspergillus* are common laboratory contaminants and for the most part may be considered as saprophytes. Some species become pathogenic and produce inflammatory granulomatous lesions in the skin, external auditory canals, paranasal sinuses, orbit, bronchi, lungs, bones, and meninges. Of the many species of *Aspergillus* only one, *A. fumigatus*, is frequently associated with disease.

Aspergilli are widely distributed in nature. Many species are pathogenic for plants; hence the spores will be found in hay, unmilled grain, and cereals. The fungus infects wild and domestic birds and animals, and insects. The disease, aspergillosis, is accordingly found in all parts of the world, but in regard to humans it occurs most frequently in those exposed often to massive doses of spores; for instance farmers contacting dust from threshers, fur cleaners employing rye flour as a grease remover, and, in France, squab feeders taking grain into their mouths for moistening.

Diagnosis

Clinical Picture: There is nothing characteristic of the infection which might lead one to clinically suspect the disease process to have stemmed from invasion by *Aspergilli*. The signs and symptoms vary with the location of the infection.

The external auditory canal is the site of the body most frequently involved.^{1, 2, 3} The skin of the canal is swollen, reddened, and dotted with crusts. There is ex-

foliation of the epithelium. The accumulation of the epithelial debris eventually causes an obstruction in the canal; accordingly there is an impairment of hearing. Quite often there follows an associated bacterial infection with the production of suppuration and pain. If the infection becomes chronic, eczematoid changes develop in the epithelium and this process extends itself to the external ear and the adjacent skin of the neck. The clinical picture of external ear disease may be produced also by species of *Mucor*, *Penicillium*, *Rhizopus*, or *Candida*.

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Isolated examples of *paranasal sinusitis*, *vaginitis*, *meningitis*, and *involvement of vertebrae and ribs* have been recorded.

Mycology: Direct microscopic examination of sputum reveals broken fragments of hyphae with many small (2 to 3 microns), round, dark green conidia.

On Sabouraud's medium at 30° C., the organism grows rapidly, appearing first as a white cottony growth. With the production of conidia the color of the colony rapidly turns to a green or dark green. Microscopic preparations should be made by carefully placing a small portion of the aerial growth in lactophenol cotton blue and covering with a cover slip. The characteristic swollen conidiophore, bearing the sterigmata and then the chains of conidia,

which may have been partially broken in making the preparation, can be identified. Species identification must be left for the mycologist.

Skin and Serological Tests: Nothing is known concerning the antibody response to infections in humans, and consequently the complement-fixation and precipitin tests remain unevaluated. Positive skin reactions to *Aspergillus* extracts, of the immediate whealing type, occur in patients with bronchial asthma, but the significance of the delayed type of reaction and its value in the diagnosis of aspergillosis are unappraised.

Treatment

The external auditory canal, when infected, must be kept dry and free from epithelial debris. Methylrosaniline Chloride Solution, N.F. (gentian violet), a 1 per cent solution in 10 per cent alcohol, should be painted over the canal after all cerumen and debris have been removed. This procedure should be repeated frequently, every week, until the infection has subsided. Metacresyl acetate (cresatin) may be employed in place of the gentian violet.

Pulmonary aspergillosis should be treated with iodides in a manner similar to that described in the chapter on blastomycosis. The prognosis is favorable if the infection is limited to the bronchi; the outlook is grievous if there is extensive parenchymal involvement with abscess formation.

Granulomatous areas, when accessible, should be excised; local abscesses must be drained. Iodide therapy should accompany the surgical procedures.

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Chapter 13

MUCORMYCOSIS

HUMAN INFECTION from species of *Mucor* are rare. Of the many species of this genus only a few, notably *M. corymbifer*, are pathogenic. Lichtheim¹ in 1884 demonstrated first the pathogenicity of two strains, *M. corymbifer* and *M. rhizopodiformis*, by producing disseminated abscess formation and subsequently death in rabbits following the intravenous inoculation of live spores.

Diagnosis

Clinical Picture: Under exceptional circumstances harmless saprophytic fungi such as the *Mucors* may become pathogenic for man, but the clinical picture that results is varied. In most of the reported cases of human infection only a single organ or system has been affected. *Pulmonary mucormycosis*^{2,3,4} is the commonest expression of the infection; yet there is no clue from the signs or symptoms that may lead one to suspect infection from *Mucor*. Infection of the *external auditory canals*⁵ is next in frequency, with involvement of the *upper air passages* and *skin*⁶ (paronychia) of rare occurrence. Gregory⁷ has reported three interesting cases with infection of the *meninges and brain*, due to invasion from the orbit. All three of the patients had uncontrolled diabetes. The diagnosis of mucormycosis in these patients could only be surmised through examination of gross and microscopic material following autopsy. The fungous infection was not suspected clinically, and the organisms were never recovered in culture form.

Mycology: The diagnosis of mucormycosis is fraught with difficulties. Cultivation of the fungus does not represent unimpeachable evidence of primary infection. The spores of *Mucor* are airborne and may become laboratory contaminants, and they may reside as saprophytes in the respiratory passages and on the skin.

The genus of *Mucor* along with *Rhizopus* belongs to the family, Mucoraceae. The Mucoraceae are commonly referred to as the bread molds; they are found abundantly in soil and manure, and on fruits and starchy foodstuffs. These molds are primitive ones with coarse, non-septate, white or gray mycelium, and brown or black conidia. The mycelium of *Mucor* and *Rhizopus* are loosely meshed and similar in appearance, but the two may be readily distinguished from one another. While both fill up a petri dish rapidly, *Rhizopus* alone attaches itself to the lid of the petri dish. The identification of species must be left to a mycologist.

Treatment

Because of the scarcity of infections from the *Mucors*, a specific form of therapy has not been developed. One must, therefore, adopt procedures that have been applied to other mycotic infections.

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Chapter 14

DERMATOPHYTOSIS

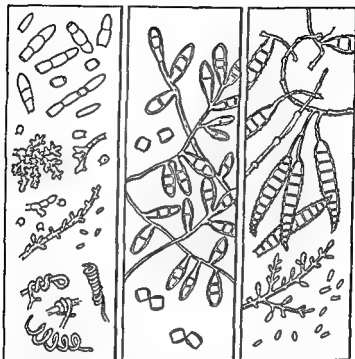
DERMATOPHYTOSIS is a more or less superficial infection of the skin and its appendages caused by anyone of the fungi known as the dermatophytes. The fungi included in the genera of *Trichophyton*, *Epidermophyton*, *Microsporum*, and *Candida* are referred to as dermatophytes. These parasites may infect many different body regions and have a wide range of morbid anatomical expressions. It is because of these two latter characteristics that so many confusing terms have invaded the literature. *Tinea*, which means "worm" in Latin, precedes *pedis*, *capitis*, *unguium*, and *cruris* on occasions to denote the regions of the body infected, and then on other occasions is used before *circinata* and *imbricata* to describe an anatomical expression of the infection.

Only one or two species of each of the four genera of dermatophytes referred to in the first paragraph are of clinical importance. *Trichophyton mentagrophytes* and *T. rubrum* commonly infect the skin and nails of the feet. *Epidermophyton floccosum* commonly infects the skin of the groin. *Microsporum Audouinii* and *M. canis* commonly infect the hairs of the scalp in children. *Candida albicans*, which also produces deep seated lesions, commonly infects the mucous membranes of the mouth and vagina, and infrequently the skin and nails.

Diagnosis

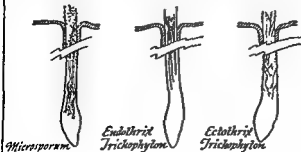
Clinical Picture: 1. *Infections of the scalp and hair* (*Tinea capitis* and *Tinea barbae*). Children are prone to develop fungous infections of the scalp, including the

The DERMATOPHYTES



Trichophyton *Epidermophyton* *Microsporum*

RELATIONS OF DERMATOPHYTES TO HAIRS



Microsporum

Endothrix
Trichophyton

Ectothrix
Trichophyton

sporum When the infection involves the groin, the organisms most likely to be responsible are *E. floccosum* or *C. albicans*.

3. *Infections of the feet and hands* (Tinea pedis)

The feet are commonly affected and the infection may express itself in a variety of ways. (A) The *chronic papulosquamous hyperkeratotic type*, unassociated with pustules and vesicles, is usually limited to the heels, soles, and sides of the feet. The scales look like bran and reside on a reddened, thickened, patchy base that is usually well demarcated, however at times the entire sole may be involved. These lesions rarely cause symptoms and may not be noticed by the patient. (B) The *chronic intertriginous type* is manifested by fissuring in the toe webs. The epidermis in the webs is white, macerated, and soggy. Hyperhydrosis is common, and the lesions give off an unpleasant odor. When the soggy epidermis is removed by scraping, the underlying base is found to be red and moist. (C) The *subacute type* is manifested by vesicles or vesicopustules extending from the intertriginous area up over the toes and feet. The soles of the feet become involved by spreading from patches of vesicles and vesicopustules. There may be isolated vesicles or bullae, and the rupture of these yields a clear, sticky fluid. Lymphangitis, cellulitis and lymphadenitis are usually the result of an extension of the subacute process. (D) The *acute type* ordinarily develops by crissipelantous spread of an eczematoid vesiculopustular nature. The vesicles contain cloudy or purulent material and may finally ulcerate. The ulcerative process may undermine the entire sole of the foot, consequently the way is paved for the eventual development of cellulitis, lymphangitis, and lymphadenitis. The acute lesions are swollen, painful, and foul to smell. Men are affected more than women. The disease is common under conditions which predispose to hyperhydrosis or

shafts and follicles of hairs. This infection disappears at the time of puberty even if it remains untreated. The first lesion is usually a small papule which is perforated by broken, dull hairs. With advancement of the infection, irregular hairless patches appear over the scalp. This type of infection is usually caused by species of *Microsporum* and *Trichophyton*, and the lesions may be either superficial or fairly deep. *Microsporum Audouini* produces superficial lesions, *M. canis*, *M. gypseum*, *T. Schoenleini*, and *T. violaceum* are the cause of lesions involving the deeper layers of skin.

Although adults rarely experience a fungous infection of the scalp as it is known in the child, they may develop a similar type of infection, caused by similar organisms, which involves the bearded region of the face. Here again as in the fungous infections of the scalp in children, there are superficial and deep infections. The superficial type of infection of the beard is usually produced by species of *Trichophyton*. The hair follicles are involved in a mild pustular lesion which tends to spread peripherally. The hairs may or may not be broken, depending upon the type of infecting organism. The deep (kerion) lesion, in which pustules and abscesses are formed about the hair follicles, is rarely observed in the United States. Species of *Microsporum* and occasionally *Trichophyton* are the etiologic agents.

2. *Infections of the smooth skin* (*Tinea corporis* and *Tinea cruris*). Both adults and children may develop an infection of the glabrous skin. The lesions which may be single or multiple begin as small, circular, reddened, scaly, maculo-papular areas that spread peripherally and heal centrally. The peripheral margin is made up of minute vesicles or pustules. Pruritus is present and if much scratching follows, eczematoid changes develop. The etiologic agents are species of *Trichophyton* and *Micro-*

is vesicular, the roof of the vesicle should be completely removed with scissors. If the hair is affected an involved hair should be epilated manually. The specimen for examination should be placed on a slide and covered with 10 per cent sodium hydroxide. Several hours must elapse to allow the sodium hydroxide to clear the specimen before making the microscopic search for hyphae.

It is desirable also to culture material from infected areas. Skin scrapings, or the roof of a vesicle, or an infected hair should be planted on Sabouraud's medium and incubated at 30° C. The identification of the fungus by its growth and microscopic cultural characteristics should be attempted only by an experienced mycologist. The isolation and classification of the fungus is an academic nicety, but is not always essential for the proper treatment of the patient. Herein, only the cultural characteristics of the common dermatophytes will be described.

1. *Trichophyton*. A *Trichophyton mentagrophytes*. The growth appears in four to six days. The cultures are powdery to granular. The color is white, but the central portion of the colony becomes buff with age. The reverse of the colony is wine-colored to brownish. The microscopic examination of the culture reveals the presence of spirals. Microconidia are borne laterally and in grape-like clusters. Chlamydospores, nodular bodies, racquet hyphae, and pectinate bodies are found. Macroconidia are rarely observed. A well-known synonym for *T. mentagrophytes* is *T. gypsum*.

B. *Trichophyton rubrum*. The growth appears in four to six days. The cultures are cottony to velvety, but sometimes develop a powdery appearance. Reddish to purple pigmentation develops on the reverse of the colony and may spread into the marginal hyphae. On microscopic examination only branched septate hyphae are found if the culture is a cottony one. Granular colonies, however,

maceration of the feet. The etiologic agents are species of *Trichophyton* and *Microsporum*, *E. floccosum*, and *C. albicans*.

The hands are less frequently involved than the feet. Any type of lesion occurring on the feet may be present also on the hands. However, the commonest expression of infection on the hands is a chronic vesiculopustular lesion involving the palms. The etiologic agents are the same as those for the feet.

4. *Infections of the nails* (*Tinea unguium*). Infection of the nails of the feet or hands begins slowly, and usually is the result of a spread from a primary infection of the skin of the feet or hands. The nails become dry, brittle, lusterless, ridged, pitted, and thickened. Detritus, made up of mycelium and desquamated cells, accumulates beneath the nails in infections caused by species of *Trichophyton* and *Epidermophyton*. Scarcely any detritus is observed in *C. albicans* infections.

Occasionally the clinical picture of chemical dermatitis and contact dermatitis simulate that of dermatophytosis. Furthermore, bacteria may produce lesions on the feet similar in characteristics to those produced by fungi. Therefore, because the diagnosis of fungous infections cannot be made with certainty in all cases on clinical grounds alone, the laboratory evidence of the presence of a dermatophyte, by microscopic examination or by culture, is essential in the scientific study of a skin affection where dermatophytosis is suspected.

Mycology: The material to be studied must be collected properly. A scalpel should be used to obtain scrapings from lesions on the smooth skin, the hands, and feet. The active edge and not the center of the lesion should be scraped, because fungous infections heal from the center. If the hyphae are to be demonstrated, they will be located in the periphery of the lesion. If the lesion

is vesicular, the roof of the vesicle should be completely removed with scissors. If the hair is affected an involved hair should be epilated manually. The specimen for examination should be placed on a slide and covered with 10 per cent sodium hydroxide. Several hours must elapse to allow the sodium hydroxide to clear the specimen before making the microscopic search for hyphae.

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will produce microconidia borne laterally and in clusters, and, occasionally, chlamydospores, nodular bodies, racquet hyphae, and macroconidia. A well-known synonym for *T. rubrum* is *T. purpureum*.

2. *Microsporum*. A. *Microsporum Audouini*. The growth appears in four to five days. The cultures are velvety with radiating furrows. The color is light gray to brown. The reverse of the colony is reddish-brown to orange. Microscopically, a few large multiseptate macroconidia, typical of the genus, are seen in primary cultures. However, these large spindle-shaped conidia are never numerous in this species and soon disappear. Microconidia are borne laterally along the hyphae. Racquet mycelium, pectinate hyphae, nodular bodies, and chlamydospores are found.

B. *Microsporum canis*. The growth appears in four to five days. The cultures are cottony and become granular or powdery in the center. The color is buff to light brown in the center. The reverse of the colony is reddish-brown to orange. Microscopically, numerous large, multiseptate, spindle-shaped, rough, thick-walled macroconidia are seen. In primary cultures an occasional small, single-celled, clavate microconidia is found. Racquet hyphae, pectinate hyphae, nodular bodies, chlamydospores and, rarely, spirals are found. Common synonyms for *M. canis* are *M. lanosum*, and *M. felineum*.

C. *Microsporum gypseum*. The growth appears in four to five days. The cultures are usually powdery, but some strains at first are woolly and later become powdery. There are radiating furrows. The color is buff to light brown. The reverse of the colony is reddish-brown to orange. Microscopically, numerous large, four to six septate, ellipsoid, rough-walled macroconidia are seen. In primary cultures a few small, single-celled, clavate microconidia are found. Racquet hyphae, pectinate hyphae,

nodular bodies, chlamydospores, and, rarely, spirals are observed.

The fact that hairs infected by *Microsporum* dermatophytes fluoresce, under filtered ultraviolet radiation, is frequently used as an aid in the diagnosis of fungous infections of the scalp in children. Inexpensive units for the production of filtered ultraviolet radiation are available on the commercial market. These units are commonly referred to as "Wood's Lights," being named for their inventor, Dr. Robert Wood, Emeritus Professor of Physics, of the Johns Hopkins University.

3. *Epidermophyton*. *Epidermophyton floccosum*. The growth appears in four to five days. The colony at first is white and granular. Later the growth becomes velvety to powdery, with radiating furrows, and the color changes to greenish-yellow. White sterile aerial mycelium develops in about three weeks and spreads over the colony. Microscopically, the large, clavate, multiseptate, smooth, thin-walled macroconidia identify the fungus. These conidia are borne singly from the hyphae or in typical clusters. There are no microconidia. Chlamydospores are abundant in old cultures. A common synonym for *E. floccosum* is *E. inguinale*.

Hypersensitivity and the Skin Test: It is important to discuss the value of skin tests in diagnosing dermatophytosis. Once the body has become infected by a fungus certain alterations occur which affect the reactivity of the tissues toward subsequent contact with the fungus or the protein of the fungus. This altered reactivity that results from infection is spoken of as "bacterial hypersensitivity," "hypersensitivity of infection," or "tuberculin type hypersensitivity." It is quite possible that an anaphylactic type of hypersensitivity to the fungus or fraction of the fungus may also develop.

Trichophytin as it is made available on the commercial

will produce microconidia borne laterally and in clusters, and, occasionally, chlamydospores, nodular bodies, racquet hyphae, and macroconidia. A well-known synonym for *T. rubrum* is *T. purpureum*.

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C. *Microsporum gypseum*. The growth appears in four to five days. The cultures are usually powdery, but some strains at first are woolly and later become powdery. There are radiating furrows. The color is buff to light brown. The reverse of the colony is reddish-brown to orange. Microscopically, numerous large, four to six septate, ellipsoid, rough-walled macroconidia are seen. In primary cultures a few small, single-celled, clavate microconidia are found. Racquet hyphae, pectinate hyphae,

dence that previous occurrences of fungus disease accounts for this type of penicillin hypersensitivity. The skin reaction to the intradermal administration of penicillin (2,000 units) in these individuals resembles in time of development and appearance a Trichophytin reaction, and this delayed reaction to the cutaneous test with penicillin is of practical importance as an aid in the diagnosis of the "spontaneous" type of reaction. The clinical picture of this spontaneous sensitivity to penicillin is that of an *erythematopapulovesicular* eruption which tends to localize first on the hands, the feet, and in the groin, and then spread over the body. This reaction must not be confused with the serum-sickness type of reaction which is also induced by treatment with penicillin.

Oidiomycin is a broth filtrate of *Candida albicans*. As it has been made available to the medical profession it has no value in the diagnosis of infections due to *C. albicans*. The term Oidiomycin is as unexact as the material which bears the name. The microorganisms that are now rightfully classed in the genus, *Candida*, have been referred to in the past as belonging to the genera of *Oldium* and *Monilia*. Such clinical manifestations of anaphylactic hypersensitivity as bronchial asthma, urticaria, and atopic dermatitis may develop during an infection from *C. albicans* (see chapter on monilliasis).

Treatment

A compound to be effective in the treatment of dermatophytosis must first possess the power to inhibit the growth of fungi or actually kill the fungi. Secondly, it must be able to penetrate the stratum corneum and come into contact with the fragments of hyphae that are embedded there. Thirdly, the compound should possess an antibacterial effect, because essentially every infection is complicated by secondary bacterial infection and

market has very limited assets. To perform the test 0.1 ml. of a 1-30 dilution of Trichophytin (Lederle) is injected intradermally and interpreted in the same manner as a tuberculin test. A positive test only indicates that at some time in the immediate or distant past the host has been infected with one or more of the *Trichophyton* fungi. A negative test is of some help in ruling out the presence of an infection with the *Trichophyton* fungi, but it must be remembered that the fungi vary in their ability to sensitize and that fungous infection without skin sensitivity to Trichophytin is possible. Also, the infecting organism may not produce antibodies that will react with the commercial Trichophytin. In other words, there may be a lack of specificity due to the genus and the species of the infecting organism. Although the immediate whealing reaction to Trichophytin has been observed and does definitely occur, there has been little thought of its significance. The immediate reaction can be assumed to be an indication of the presence of anaphylactic hypersensitivity, and it may be that the development on the part of the host of anaphylactic hypersensitivity explains the aptitude to develop concomitantly with the fungous infection such clinical manifestations of anaphylactic hypersensitivity as urticaria, purpura, migrating phlebitis, erythema nodosum, and papular and eczematoid eruptions. When these eruptions occur along with and as a result of dermatophytosis, they are spoken of as dermatophytids.

The *Trichophyton* fungi play a role in the development of "spontaneous" allergic reactions to penicillin. It has been fully demonstrated that several strains of *Trichophyton mentagrophytes* elaborate antibacterial substances similar in some respects to penicillin. This fact may be of significance in explaining the "spontaneous" allergic eruptions to penicillin, because there is increasing evi-

and there are fissures and maceration without acute inflammation, Desenex, Sopronol, or Asterol ointment should be employed. There is essentially no difference in the clinical effectiveness of these three ointments. The selected ointment should be applied with massage over the toes, between the toes, and under the toes every night. The following morning the ointment should be removed with soap and water or with a towel, and the feet dusted with Desenex, Sopronol, or Asterol powder. Some of the powder should also be dusted into the shoes. Therapy must be continued until the lesions have completely healed, and then continued for several weeks thereafter.

When hyperkeratosis is present a keratolytic preparation such as Whitfield's ointment (salicylic acid 3 per cent, benzoic acid 6 per cent) should be massaged into the affected areas every night. The concentration of salicylic acid in the ointment may be increased in resistant infections such as those caused by *T. rubrum*, provided the weaker preparation has been tolerated with impunity.

Long standing chronic infection of the soles of the feet with marked hyperkeratosis often responds to treatment with an ointment of 45 per cent salicylic acid and 5 per cent starch in petrolatum base. On two successive nights a layer of ointment $\frac{1}{8}$ inch in depth is spread over the involved area which in turn is covered with a bandage. The bandage and the ointment are removed in the morning. Washing of the feet is not permitted. An inflammatory reaction to this ointment occurs rather frequently.

Prophylactic measures to prevent recurrence of infection are strongly advised. Footwear should be treated with formalin vapor. The shoes or slippers and a wide-mouthed jar filled with absorbent cotton are placed in a shoe box. The jar is filled one-quarter full with formalin, and the lid of the box sealed on with Scotch tape. Care

the hypersensitive reaction to this bacterial infection. Fourthly, the compound and the vehicle in which it is placed should be neither irritating nor sensitizing.

1. *Infections involving the skin.* During the *acute inflammatory stage*, bed rest and the application of wet dressings or mild soaks are indicated. When the lesions are present on the hands and/or feet, warm potassium permanganate soaks (1:3,000) for 30 minutes, four times a day, should be employed. When the lesions are not accessible for soaks, a continuous wet dressing of boric acid solution (4 per cent) is recommended. As the acute process subsides the frequency of the soaks may be decreased, and the wet dressings may be applied at intervals with gradually increasing rest periods. When the exudative and inflammatory reaction is minimal, the soaks and wet dressings may be discontinued and mild fungicidal ointments applied. The following ointments are recommended and rarely cause irritation: undecylenic acid ointment (Desenex or Timofax), propionic and caprylic acid ointment (Sopronol), and Asterol ointment.

Blebs and vesicles should be opened. This hastens healing and relieves discomfort. Dermatophytids, especially of the hands, are frequently encountered in the acute inflammatory stage when *T. mentagrophytes* is the etiological agent. Fungicidal therapy is not indicated as these lesions of hypersensitivity disappear as soon as the primary infection is cured. Potassium permanganate soaks (1:3,000), or boric acid (4 per cent) wet dressings are suggested. As soon as the lesions become dry, and the exudative stage has subsided, a zinc oxide ointment containing 3 per cent ichthyol may be applied two or three times daily.

The treatment of *chronic lesions* varies with the type of pathologic process encountered. When hyperkeratosis (thickening of the horny layer of the epidermis) is slight,

3. *Infections of the scalp and hair.* Infections caused by *M. canis* and *M. gypseum* do not resist treatment, do not require x-ray epilation, and usually are cured spontaneously. Any mild fungicidal ointment such as Desenex, Sopronol, Asterol, or 1 per cent ammoniated mercury may be employed to help loosen the hair and prevent spread of the infection. The head should be shampooed daily with a mild soap and a soft brush to remove infected and loose hairs.

Infections caused by *M. Audouini* and the *Trichophyton* species are resistant to treatment; thus epilation is usually advisable. If the condition is noninflammatory, x-ray epilation under the direction of a dermatologist or radiologist thoroughly trained in the technique is indicated. Following radiation therapy, ammoniated mercury ointment (3 per cent) is applied to the scalp every night, and a linen cap worn until the hairs become loose. This occurs about three weeks after radiation, then a daily shampoo using a mild soap and a soft brush is recommended to remove the loosened hairs. Remaining infected hairs may be removed manually, or by placing warmed adhesive tape strips over the scalp. At this time the ammoniated mercury ointment is replaced by salicylanilide (5 per cent), Desenex, Sopronol, or Asterol ointment. One of these latter preparations should be massaged into the scalp every night. The patient is not dismissed as cured until the "Wood's light" examination is negative on two successive examinations, made at weekly intervals.

When the beard is involved and there is an associated inflammatory reaction, wet dressing of normal salt solution or boric acid (4 per cent) should be applied until this phase of the infection has subsided. Infected hairs should then be manually epilated, once weekly. The "Wood's light" is helpful in locating involved hairs. Fungi-

must be taken so that the formalin does not spill on the shoes. After 24 hours the footwear is removed and aired for 48 hours before use. Cotton socks should be boiled 10 minutes after each use. The tub or shower stall should be washed several times a week with 2 per cent cresol solution. Disposable paper slippers should be used for walking to and from the bathroom. The patient should be warned against scratching an infected area with the fingers as an infection of the finger nails may be the result.

2 *Infections involving the nails.* Because treatment and prognosis vary with the causative organism, a cultural differentiation of the infecting organism is desirable. Infections from *T. mentagrophytes* respond to milder medications and in a shorter period of time than infections from *T. rubrum*.

If the nails are only slightly involved the patient should be instructed concerning the use of a file, and the technique of removing detritus. The nails must be kept paper thin by filing every day. Following each period of filing an ointment of salicylic acid (6 per cent) and benzoic acid (12 per cent) should be massaged into the nail. Prolonged contact of the nail with the ointment can be provided by applying an adhesive plaster cap over the nail. If this is done it is advisable to protect the surrounding skin by the application of compound tincture of benzoin. Salicylic acid plaster (40 per cent) cut to nail size and applied every day is often helpful.

The infections of the nails are very resistant to treatment; therefore, a therapeutic regime must be carried out over a period of many months. Evulsion of the nail should be limited to cases in which *T. rubrum* is the infecting organism, where there is no active infection of the surrounding skin, and where all other methods of therapy have failed.

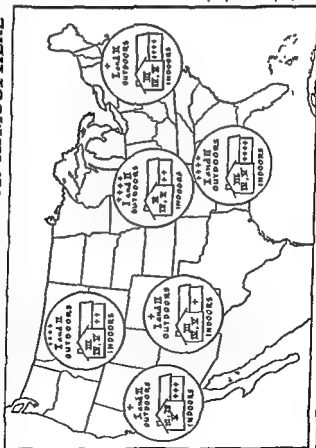
3. *Infections of the scalp and hair.* Infections caused by *M. canis* and *M. gypseum* do not resist treatment, do not require x-ray epilation, and usually are cured spontaneously. Any mild fungicidal ointment such as Desenex, Sopronol, Asterol, or 5 per cent ammoniated mercury may be employed to help loosen the hair and prevent spread of the infection. The head should be shampooed daily with a mild soap and a soft brush to remove infected and loose hairs.

Infections caused by *M. Audouini* and the *Trichophyton* species are resistant to treatment, thus epilation is usually advisable. If the condition is noninflammatory, x-ray epilation under the direction of a dermatologist or radiologist thoroughly trained in the technique is indicated. Following radiation therapy, ammoniated mercury ointment (3 per cent) is applied to the scalp every night, and a linen cap worn until the hairs become loose. This occurs about three weeks after radiation, then a daily shampoo using a mild soap and a soft brush is recommended to remove the loosened hairs. Remaining infected hairs may be removed manually, or by placing warmed adhesive tape strips over the scalp. At this time the ammoniated mercury ointment is replaced by salicylanilide (5 per cent), Desenex, Sopronol, or Asterol ointment. One of these latter preparations should be massaged into the scalp every night. The patient is not dismissed as cured until the "Wood's light" examination is negative on two successive examinations, made at weekly intervals.

When the beard is involved and there is an associated inflammatory reaction, wet dressing of normal salt solution or boric acid (4 per cent) should be applied until this phase of the infection has subsided. Infected hairs should then be manually epilated, once weekly. The "Wood's light" is helpful in locating involved hairs. Fungi-

cidal ointments are rubbed into the bearded area twice daily. For this purpose either ammoniated mercury (10 per cent), Sopronol, Desenex, or Asterol ointment is suggested. Shaving is prohibited. The beard may be trimmed with scissors. X-ray epilation is usually not necessary.

*The CONCENTRATION of the PREDOMINATING
MOLDS in INDOOR and OUTDOOR ATMOSPHERE*



Chapter 15

SPORES OF SAPROPHYTIC FUNGI AS ALLERGENS

THE SPORES OF SOME saprophytic fungi, just as the pollens of trees, grasses, and weeds, are capable of setting off allergic reactions in the respiratory passages producing rhinitis and asthma, and in the skin producing lesions of atopic dermatitis.

The spore content of the indoor and outdoor atmosphere varies somewhat in concentration and in character depending upon climatic conditions. The concentration of the mold content of indoor atmosphere is higher in damp, warm and humid localities, than in dry and warm or in dry and cold areas. The concentration of molds in the outdoor atmosphere is higher in agricultural areas during the growing season of vegetation, than along the coastal regions. The fact that climatic conditions affect the atmospheric concentration of the mold spore content has led many investigators in Holland, Spain, Denmark, Sweden, and the United States to incriminate molds as a cause for "climatic asthma." The mold spore counts of outdoor atmosphere have been studied in many sections of the United States at regular intervals since 1933. Regardless of where the mold spore counts have been made there is a certain uniformity in regard to the genera that are most prevalent. *Penicillium*, *Aspergillus*, *Hormodendrum*, *Alternaria*, *Mucor*, and *Rhizopus* predominate in the United States as well as abroad. It is generally conceded that *Penicillium*, *Aspergillus*, and sometimes, *Mu-*

cor predominate mostly indoors, while *Hormodendrum* and *Alternaria* predominate outdoors.

The potentiality of mold spores as excitants of inhalant allergy is actuated by their buoyancy. The average diameter of such spores ranges from 3 to 5 microns, whereas the diameter of common airborne pollens varies from 15 to 40 microns. *Alternaria* and *Hormodendrum* spores, originating in southern Minnesota have moved with air masses as far east as New York City and as far south as Oklahoma City in 24 hours. Aviators have recovered plant disease spores at altitudes of 18,000 feet. Furthermore, it has been demonstrated that the spores of *Hormodendrum* may be carried in great numbers throughout large buildings within a few minutes after they have been liberated in a single room, and that these spores entered in large numbers all of the rooms of the building in which air itself had free access. These data serve to impress upon us the potential ubiquity of molds and their spores.

Sixty-six valid species of the genus *Aspergillus*, and over 600 species of the genus *Penicillium* have been described. There are only a few mycologists who are qualified to attempt the identification and classification of all the species of these two genera. It is for this reason that no attempt is made to differentiate species of *Aspergilli* or *Penicillia* in the conducting of mold surveys.

Penicillia are characterized by the production of conidia from sterigmata, which in turn are produced in clusters or whirls referred to as verticils. Verticils come off of short branches called metulae. Depending upon whether there are one or more metulae, and whether or not they are arranged symmetrically or asymmetrically, the *Penicillia* are classified.

The word *Aspergillus* means a special type of brush used for the sprinkling of holy water, and the name of the genus has derived its origin from the fact that the

conidia (spores) are arranged so as to resemble the appearance of a brush. The conidiophore, or the spore bearing portion of the mycelium, is made up of a foot cell, which is simply an enlarged mycelial cell, the stalk, the swelling at the end of the vesicle, and the chains of conidia. Between the vesicle and the conidia are little stalks known as sterigmata. The conidia arise from the sterigmata. In some species of this genus secondary sterigmata come off of the primary ones, and in these species the conidia arise from the secondary sterigmata. Mycelium and conidia may be colored, and the color offers assistance in identification.

Aspergillus and *Penicillium* species are found on a variety of substrates. They are abundant in soil and on dried vegetable matter, such as hay and grains. *Aspergillus*, unlike *Penicillium*, tolerates high temperatures. Because of the abundant number of species of these genera, the routine skin testing with a few isolated species of *Aspergillus* or of *Penicillium*, acquired from some biological company, is a demonstration of ignorance and folly on the part of the skin tester. If allergy to molds is suspected, a study of the patient's own atmosphere and a preparation of extracts from these molds in his atmosphere is essential.

Cladosporium and *Hormodendrum* were at one time considered as names for two different genera. The name *Hormodendrum* unfortunately predominates over *Cladosporium* in the medical literature, even though *Cladosporium* by reasons of priority is the correct name for the genus. A small, dark, olive-green, velvety colony of *Cladosporium* is familiar to anyone who has manifested even a meager interest in molds. These molds are found in the soil, on decaying leaves and straw, and on other vegetation. They are considered to be of some importance in the spoilage of malt and of stored tobacco. *Cladosporium*

herbarum is the species of this genus which is most commonly isolated. *Cladosporium pulcum*, the tomato mold, has caused asthma in greenhouse tomato growers.

Members of the genus *Alternaria* form dark, olive-green, or brown colonies similar to those of *Cladosporium*; yet the colonies are looser and more woolly in type. Molds of this genus are characterized by the large multi-chambered spores which occur in chains and sometimes have segments of mycelium between them. Species of this genus, as the species of *Cladosporium*, are common plant pathogens. It is undeniable that these molds occur in the greatest multitude throughout agricultural regions, and in these areas they may act as excitants of inhalant allergy.

Mucor and *Rhizopus* are the two genera of the Phycomycetes that are of interest to the clinician and the bacteriologist. Both molds fill up a petri dish with mycelium, but *Rhizopus* covers the agar rapidly, climbs up the side of the dish, and attaches itself to the undersurface of the lid by holdfasts which are also known as Rhizoids. *Rhizopus nigricans*, by far the most common air contaminant, is important in the spoilage of fruits, especially stored sweet potatoes. Strawberries are also susceptible, and the fungus is responsible for the disease known as leak, causing softening and dripping of the fruit. There are many species of *Mucor*. They are commonly referred to as the bread molds, and are found abundantly in soil, manure, starchy foodstuffs, and on fruit. Along with *Rhizopus* they give rise to loosely meshed aerial mycelia which may be gray or white in color.

The smuts and rusts belong to the class of Basidiomycetes and are plant parasites. Nearly everybody is familiar with the appearance of an ear of corn that has been affected with the corn smut, *Ustilago Leae*, and the disease of wheat known as black stem rust which is caused

by the rust, *Puccinia graminis*. Other grains are similarly affected by rusts and smuts, and the spores of these plant parasites are capable of producing allergic reactions in the respiratory passages.

There is the possibility that molds make up a part of the protein content of crude house dust, and an attempt is being made by several workers in this country and abroad to determine the role of mold allergy in patients with so-called house dust sensitivity. The colossal amount of work and knowledge that is required to shed light upon the fungi as excitants of inhalant allergy is enough to dim the enthusiasm of even the most ardent of investigators, and it is perhaps for this reason that our understanding in its regard is still so very limited.

Chapter 16

POISONOUS FUNGI

MYCETISMUS

MOST OF THE EDIBLE and poisonous species of fungi belong to the class Basidiomycetes; however a few are Ascomycetes. For the benefit of the amateur mycophagist who seeks to embellish his diet with personally gathered mushrooms, it is important to emphasize that there is no simple rule or characteristic such as excellent flavor, failure to tarnish a silver coin, or an easily peeled cap, which distinguishes the edible from the poisonous species. The only safe basis for selecting edible from inedible species is a thorough acquaintance with the species collected.

Of the Basidiomycetes, *Amanita phalloides*, *A. verna*, *A. virosa*, *A. pantherina*, and *A. muscaria* are the fungi commonly responsible for mycetismus (mushroom poisoning). Of these five fungi, the first three, that is *A. phalloides*, *A. verna*, and *A. virosa* are closely related and cause the same type of poisoning. Since their effect is delayed they may be considered as the delayed poisonous fungi. The other two species, *A. pantherina* and *A. muscaria*, cause a rapid type of poisoning; the symptoms come on within a few minutes to two hours after ingestion. They may be considered then as the rapidly poisonous fungi.

More than 90 per cent of the recorded deaths from fungus poisoning are caused by *A. phalloides*. This fungus, though fairly rare in the United States, is common in the woods of Britain and Western Europe. Referred to as the "death cup," it is characterized by the cup-shaped envelope (volva) about the base of the stem,

and the ring or collar about the stem near the cap. The cap, which is olive or yellowish-green in color with a darker center, measures about 8 cm. in diameter, and sets upon a stem that is about 10 cm. long

The characteristic features of *A. phalloides* poisoning are well marked. An incubation period of about six to 15 hours is followed by the sudden onset of such gastrointestinal symptoms as: abdominal pain, nausea, vomiting, and the passing of watery stools that usually contain blood and mucus. There is also extreme thirst with anuria. Jaundice appears in two to four days after the onset of the intestinal symptoms. Cramps in the calves of the legs with coldness of the extremities and cyanosis are part of the picture. After about five to eight days the patient becomes comatose and death follows soon thereafter. *A. verna* and *A. virosa* produce the same clinical picture.

Amanita muscaria and *A. pantherina* are both responsible for poisoning of a different type. They act especially on the nervous system. Gastro-intestinal symptoms, though present, are of secondary importance. The poisonous effects of *A. muscaria* are due to muscarine. This alkaloid is a choline derivative, and like acetylcholine stimulates the activity of the effector cells in organs innervated by cholinergic nerves. Unlike acetylcholine it neither stimulates the contraction of skeletal muscle nor acts upon the autonomic ganglia.

A. muscaria is generally well known because of its bright scarlet, or orange-red cap. On the surface of the cap are scattered whitish, wart-like masses. There is a well developed ring and a poorly developed volva. The color of the cap of *A. pantherina* varies from yellowish-brown to brownish-gray. The stem is white with a bulbous base which shows the remains of a volva. The ring near the cap does not persist.

Poisoning from *A. muscaria* and *A. pantherina* comes on within a period of a few minutes to several hours after eating. There is salivation and lacrimation. The pupils are contracted and fail to react to light and accommodation. Nausea, vomiting, and abdominal pain with diarrhea are common. The pulse is normally slow and irregular. Dizziness, mental confusion, convulsions, and coma appear in severe cases. In the fatal cases, death occurs within a few hours.

The cherished edibles among the larger Ascomycetes are the truffles (underground fruit of the fungi in the genus *Tuber*), and the morels (fungi belonging to the genus *Morchella*). Rather similar to the fungi belonging to the genus *Morchella* is the fungus, *Gyromitra esculenta*. This fungus, which causes poisoning that may be fatal, has a convoluted cap which is rather fawn-colored while young but which becomes dark chestnut as it matures. The stem is white and somewhat flattened. If the fungus is cooked the toxic properties are destroyed. There is a long incubation period after eating before the onset of symptoms. An interesting observation has been that quite often the fungus can be initially eaten with impunity, and that the symptoms of poisoning follow the second fungus meal if it is taken soon after the first. The manner in which the fungus poisons, and the symptoms that are produced are identical to those already described for *Amanita phalloides*. It may well be classed as a delayed poisonous fungus.

Treatment

Delayed Type of Poisoning: There is no known specific therapy. The stomach should be emptied promptly by lavage. Magnesium sulfate, 60 ml. of a 50 per cent solution, should be employed and some of this solution left in the stomach to promote catharsis. Colonic irriga-

tion is likewise suggested. Diuresis should be stimulated by the frequent intravenous administration of 10 per cent glucose solution. If there is evidence of hemolysis of red blood cells (one of the toxic principles of *A. phalloides* is an hemolysin), blood transfusions in amounts necessary to compensate for this are indicated. With the thought that cortisone or corticotropin might protect the effector cells from the toxins of the fungi, large doses of either are recommended. If restlessness or excitement becomes serious, morphine sulfate, 8 mg. subcutaneously, is helpful. Adequate relief for severe excitement may require the intravenous administration of sodium pentobarbital, 0.1 to 0.2 gm. dissolved in 10 ml. of normal saline. The vomiting, diarrhea, and abdominal colic are treated in the same manner as an enteritis produced by a virus or bacterium.

Rapid Type of Poisoning: The symptoms are due to the alkaloid muscarine. The prognosis is good even in severe cases if atropine is administered. A dose of 2 mg., subcutaneously, should be given promptly and repeated at intervals until there are moderate toxic effects. Other therapeutic measures as enumerated in the paragraph on the treatment of the delayed type of poisoning may be instituted, if required.

ERGOTISM

The spores of the ergot fungus, *Claviceps purpurea*, infect flowers of cereals, especially rye, and of grasses. As a result, the ovary of the plant is destroyed and the "seed" replaced by a compact mass of hyphae which projects from the ear as a small, dark, horn-like structure. This compact mass of hyphae is called a sclerotium.

The sclerotia, when derived from rye, constitute the commercial source of ergot. Ergot is a veritable storehouse of alkaloids but only two, ergotamine and ergonovine, are important clinically.

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Ergot poisoning, which is now rare in man, has been recognized since 944 A.D. The name of St. Anthony's Fire was assigned to epidemics in 944 and 1090. St. Anthony was the Saint to whom the individual suffering from ergotism pleaded for succor. The "Fire" was suggested from the symptoms of affected individuals who complained of an intense burning sensation throughout their bodies.

Two types of ergotism, the convulsive and the gangrenous, have been distinguished by scientists and historians who have written on the subject. The gangrenous type was prevalent in France, west of the Rhine river. The convulsive type occurred particularly in Russia, and in the lands to the east of the Rhine river. It has been suggested that the prevalence of the severe convulsive type of ergotism in Germany and Russia was due to a basic vitamin A deficiency in the diet. Such a deficiency did not exist in France.

The gangrenous type of ergotism affects the hands and feet. Vascular stasis causes drying and mortification of the tissues. The dead, dried joints break off without bleeding. In the convulsive type the patient suffers from periodic convulsive seizures of the extremities. The accompanying pain is excruciating, and has been described as "burning" and "like fire."

Improved agriculture procedures and a generalized alerting of farmers and ranchers to the dangers of ergotized rye have nearly obliterated epidemics of ergotism. Nevertheless, ergotism is still of historical interest, and the symptoms of ergot poisoning may be observed in modified forms throughout the study of the pharmacologic actions of the ergot alkaloids.

SUBJECT INDEX

A

Abdominal organs, actinomycosis
in, 8

Abscess

actinomycotic hepatic, 9
formations in histoplasmosis, 44
in brain, 14
in kidneys, 33
in liver, 33
in spleen, 33
subcutaneous in sporotrichosis,
56

Acneform type of sporotrichosis, 56

Actinomyces bovis, 6

Actinomyces Israeli, 6
mycology of, 10

Actinomycetaceae

genus *Actinomyces* anaerobic, 5
genus *Nocardia* aerobic, 5

Actinomycetales

key to family and genera of order
of, 5
resemblance to *Nocardia*, 6

Actinomycetes

acid-fast, infections from, 12, 13,
14
cause of mycetoma pedis, 15
human infections from, 5-20
similar to tubercle bacillus, 14

Actinomycosis

abdominal type, 8
Actinomyces Israeli, 7, 8
cervico-facial, 7, 8
diagnosis of, 8
differential diagnosis in
nocardiosis, 13
North American blastomycosis, 30

in reference to

Actinomyces bovis, 6

Actinomyces Israeli, 6

non-specific measures of treat-
ment in, 12

pulmonary, 9

roentgen irradiation in treatment
of, 12

surgical excision in, 11

treatment of, 11, 12

therapeutic drugs in treatment of
aureomycin, 11

chloramphenicol, 11

penicillin, 11

potassium iodide, 11

sulfadiazine, 11

sulfamerazine, 11

Actinomycotic hepatic abscesses, 9
"Acute miliary pneumonitis," 43

Albicans, 73

Alkalinization, in treatment of
cryptococcosis, 70

Allergens, spores of saprophytic
fungi, 118-123

Allergic eczema in moniliasis, 78

Alternaria, 118, 119, 120, 122

Amanita muscaria, 124, 125, 126

Amanita pantherina, 124, 125

Amanita phalloides, 124, 125, 126,
127

Amanita verna, 124, 125

Amanita virosa, 124, 125

Anunoniated mercury ointment,
115

Anaerobic *Actinomyces*, cultural
differences in, 6

Anal pruritus, 74

- Anemia**
 hyperchromic, 33
 in histoplasmosis, 45
- Appendix, actinomycosis in, 9**
- Arthralgia, 21, 23**
- Arthrospores, 26**
- Ascomycetes, 3, 4, 124, 126**
 fungi, 3
 in ascus, 4
 plant pathogens of, 4
- Aspergillosis, 91-97**
 diagnosis of, 91, 95
 infection in external auditory canal, 91, 95
 iodide therapy in, 96
 metacresyl acetate in treatment of, 96
 methylrosaniline in treatment of, 96
 mycology of, 96
 prognosis of, 96
 skin and serological tests in, 96
 treatment of, 96
- Aspergillus, 94, 95, 118, 119, 120**
- Aspergillus fumigatus, 94, 95**
- Asterol ointment, 112, 113, 115, 116**
- Asthma, "climatic," 119**
 in moniliasis, 77
- Asymptomatic pulmonary form of histoplasmosis, 42**
- Aureomycin**
 in treatment of
 actinomycosis, 11
 nocardiosis, 17
- B**
- Bacterial hypersensitivity, 109**
- Basidiomycetes, 122, 124**
 minute forms
 plant parasites, 4
 rusts, 4
 smuts, 4
 mushrooms and puffballs, 4
- Benign pulmonary type histoplasmosis, 42**
- Black hairy tongue, 74**
- Blastomyces**
brasiliensis, 90, 91, 92
dermatitidis, 31, 34, 37, 46, 91
 vaccine, 69, 90
 method of preparation, 35, 36
 reactions to, 34
- Blastomycosis**
 desensitization therapy of, 35
 differential diagnosis in
 actinomycosis, 7
 cryptococcosis, 67
 nocardiosis, 13
 North American type (*see*
 North American blastomycosis)
 pulmonary, management of, 35
 South American type (*see* South
 American blastomycosis)
 systemic, management of, 35
- Blood stream, metastasis of, 9, 32**
- Boeck's sarcoid**
 differential diagnosis in cryptococcosis, 66
 in cryptococcosis, 67
- Bones and joints, infection of, 9, 25, 33, 67**
- Boric acid, 115**
- Brewer's thioglycollate media, 10**
- Bronchial asthma in moniliasis, 77**
- Bronchitis,**
 in cryptococcosis, 65
 in geotrichosis, 82
 in moniliasis, 76
- Bronchogenic carcinoma, 32**
- Bronchopneumonia, 77**
- Bronchopulmonary moniliasis, 76**
 treatment of, 80
- Budding cells, 75, 76**
 examination of, in moniliasis, 79
- C**
- California disease, 22**
- Candida, 95, 103, 111**

- albicans*, 72, 73, 74, 75, 76, 77, 78, 79, 103, 105, 106, 111
 genus, 77
Guilliermondi, 73, 77
Krusci, 73
parakrusci, 73, 77
pseudotropicalis, 73
stellatoides, 73, 79
tropicalis, 73
- Capitis, 103
 Caprylic acid ointment, 112
 Caprylic Compound, N.N.R., 80
 Carcinoma
 bronchogenic, 32
 differential diagnosis in cryptococcosis, 68
 Cecum, actinomycosis in, 9
 Central nervous system, infection in, 63
 Cerebrospinal cryptococcosis, 63
 Cerebral (fatal) type cryptococcosis, 60
 Children, hair and scalp infection of, 104
 Chlamydo-spores, 26, 107, 108, 109
 Chloramphenicol, 11
 Chromoblastomycosis, 86-89
 diagnosis of, 87, 89
 potassium iodide in treatment of, 89
 prognosis of, 89
 skin and serological tests, 88, 89
 treatment of, 89
 x-ray therapy in, 89
Cladosporium, 121, 122
Cladosporium herbarum, 122
Cladosporium pulvum, 122
 Classes of fungi,
 Ascomycetes, 3
 Basidiomycetes, 3
 Imperfecti, 3
 Phycomycetes, 3
Claviceps purpurea, 127, 128
 "Climatic" asthma, 122
 Coccidioidal granuloma, III
Coccidioides immitis, 21-28, 34, 91
 (see also coccidioidomycosis)
 Coccidioidin skin test, 24, III
 Coccidioidomycosis, 20-28
 contagious, 28
 differential diagnosis in
 actinomycosis, 7
 common cold, 20
 cryptococcosis, 67
 drug eruptions, 20
 encephalitis, 20
 influenza, 20
 measles, 20
 North American blastomycosis, 30
 pneumonia, 20
 poliomyelitis, 20
 scarlet fever, 20
 tuberculosis, 20
 geographical locations of, 21
 laboratory studies in, 23, 24
 mycology of, 26
 physical findings in, 23
 primary type, 22
 prognosis of, 27
 progressive or disseminated type, 24, 25
 roentgenograms of lungs in, 23, 25
 skin and serological tests in, 24, 26
 symptoms of, 23, 25
 treatment of, 27
 Coccidiosis, protozoan infection, 22
 Common cold, 20
 Complement-fixation test for coccidioidomycosis, 24, 26
 histoplasmosis, 46
 moniliasis, VII
 North American blastomycosis, 34, 35
 Concentration of saprophytic molds, 118
 Conjunctivitis, phlyctenular, 23

- Corticotropin, 127
 Cortisone, 127
 Cruris, 103
 Cryptococcosis (torulosis), 60-71
 alkalinization in treatment of, 70
 areas found in, 62
 central nervous system, infection in, 63
 cerebral type (fatal), 60
 cerebrospinal, 63
 clinical course of, 64, 65
 clinical picture of, 62, 63
 diagnosis of, 62, 63
 differential diagnosis in
 Boeck's sarcoid, 66
 carcinoma, 66
 hydatid cyst, 66
 meningitis, 65
 nocardiosis, 13
 North American blastomycosis, 30
 pulmonary tuberculosis, 66
 discovery of, 61
 hyperthermia in treatment of, 70
 infections of
 bones and joints in, 67
 lymphatic system in, 66, 67
 respiratory system in, 65, 66
 skin and mucous membranes in, 67
 laboratory picture in, 67, 68
 lymphadenopathy in, 63
 meningo-encephalitis in, 63
 mycology of, 68, 69
 prognosis of, 64, 65, 69
 pulmonary type, 60
 roentgenogram of lungs in, 65, 67
 skin and serological tests in, 69
 source of, 61, 62
 symptoms of headache, 63
 treatment of, 69, 70
 x-ray findings in, 66
 x-ray irradiation in treatment of, 70
 Cryptococcus neoformans (*Torula histolytica*), 61
 Crystalline procaine penicillin, 11
 Cutaneous blastomycosis with allergy, 35
 Cutaneous blastomycosis without allergy, 35
 Cutaneous moniliasis (*see* Moniliasis, infection of skin)

D
 Dermatophytes
 hypersensitivity in, 109, 110, 111
 skin test in, 109, 110, 111
 Dermatophytosis, 102-116
 diagnosis of, 103-111
 hyperhidrosis in, 105
 infections of
 feet and hands, 104
 nails, 106
 scalp and hair, 103
 smooth skin, 104
 mycology of, 106-111
 prophylactic measures to prevent reinfection, 113, 114
 treatment of, 111-116
 nails, 114
 scalp and hair, 115, 116
 skin, 112, 113, 114
 Desener, 112, 113, 115, 116
 Desert fever, 21
 Desert rheumatism, 21
 Diabetes mellitus, 98
 infection of skin in moniliasis, 76
 Diagnosis of
 actinomycosis, 8
 aspergillosis, 94
 chromoblastomycosis, 87
 coccidioidomycosis, 22
 cryptococcosis, 62, 63
 dermatophytosis, 103, 111
 ergotism, 128
 geotrichosis, 82
 histoplasmosis, 42-47

moniliasis, 75
 mucormycosis, 93
 mycetismus, 125
 North American blastomycosis,
 32-34
 South American blastomycosis,
 91
 sporotrichosis, 54, 55

Diarrhea, 74
 Discovery of sporotrichosis, 53
 Disease provoking fungi, 3
 Disseminated type of histoplas-
 mosis, 45
 Drug eruption, differential diag-
 nosis in coccidioidomy-
 cosis, 20

E

Ectothrix *Trichophyton*, 102
 Eczema, allergic, 78
 Eczematoid dermatitis, 78
 Elephantiasis, 83
 Encephalitis, 20
 Endocarditis, mycotic, 77
 Endocardium, lesions of, 10
 Endothrix *Trichophyton*, 102
 Epidemic of sporotrichosis, 54
 Epidermophyton, 102, 103, 106
 floccosum, 103, 105, 106, 109
 microscopic examination of,
 109
 inguinale, 109
 Ergonovine, 127
 Ergotamine, 127
 Ergot fungus, 4
 Ergotism, 127, 128
 Erythema, 40
 in histoplasmosis, 45
 multiforme, 21, 23
 nodosum, 21, 23
 Erythematopapulovesicular erup-
 tion, 111
 Ethyl vanillate, 47, 48
 External auditory canal

diagnosis of aspergillosis in, 94,
 95
 mucormycosis in, 93

F

Fallopian tubes, actinomycosis in, 9
 Feet, infections of, 105
 Fever
 desert, 21
 irregular in histoplasmosis, 41
 San Joaquin, 21
 septic in histoplasmosis, 45
 valley, 21
 Filaments, 75, 76
 Fungus, fungi
 Actinomyces bovis, 6
 Actinomyces israeli, 6
 mycology of, 10
 Albicans, 73
 Alternaria, 118, 119, 120, 122
 Amanita muscaria, 124, 125
 Amanita pantherina, 124, 125
 Amanita phalloides, 124, 125,
 126, 127
 Amanita verna, 124, 125
 Amanita citrosa, 124, 125
 Aspergillus, 94, 95, 118, 119, 120
 Aspergillus fumigatus, 94, 95
 Candida, 95, 103, 111
 Candida albicans, 72, 73, 74, 75,
 76, 77, 78, 79, 103, 105,
 106, 111
 Candida Guilliermondii, 73, 77
 Candida Krusei, 73
 Candida parakrusei, 73, 77
 Candida pseudotropicalis, 73
 Candida stellatoidea, 73, 77
 Candida tropicalis, 73
 Cladoporium, 121, 122
 Cladoporium herbarum, 122
 Cladoporium pulvum, 122
 classes of
 Ascomycetes, 3
 Basidiomycetes, 3
 Imperfecti, 3

- Phycomycetes, 3
Claviceps purpurea, 127, 128
Coccidioides immitis, 21-28, 91
Cryptococcus neoformans, 61
 disease provoking, 3
Ectothrix Trichophyton, 102
Endothrix Trichophyton, 102
Epidermophyton, 102, 103, 106
Epidermophyton floccosum, 103, 105, 106, 109
Epidermophyton inguinale, 109
 ergot, 4
Geotrichum, 82, 83, 84
 growth of, 3
Gyromitra esculenta, 126
Histoplasma capsulatum, 40, 41
Hormodendrum, 87, 118, 119, 120, 121
Imperfecti, 4
Microsporum, 102, 103, 104, 106, 108-116
Microsporum Audouinii, 103, 104, 108, 115
Microsporum canis, 103, 104, 108
Microsporum felineum, 108
Microsporum gypseum, 104, 107, 108, 109, 115
Microsporum lanosum, 108
Monilia, 73, 111 (*see Candida*)
Monilia albicans, 73 (*see Candida albicans*)
Morchella, 126
Mucor, 4, 95, 118, 119, 122
Mucor corymbifer, 98
Mucor rhizopodiformis, 98
Nocardia asteroides, 14, 15
Nocardia maduræ, 13, 16
Nocardia Mexicana, 13, 16
 nonpathogenic, 3
oidiomycin, 111
Oidium, 111 (*see Candida*)
Paracoccidioides brasiliensis, 91
Penicillia, 120
Penicillium, 95, 118, 119, 120
Phialophora campactum, 86, 88
Phialophora Pedrosot, 86, 88
Phialophora verrucosa, 86, 87, 88
 poisonous, 124-128
Puccinia graminis, 123
Rhizopus, 4, 95, 99, 119, 122
Rhizopus nigricans, 122
 rodents as reservoirs for, 23
 saprophytic, 3, 119
Serratia marcescens, 27
 spores of saprophytes as allergens, 118-123
Sporothrix Schenckii, 53
Sporotrichum Beurmanni, 53
Sporotrichum Schenckii, 53
Torula histolytica, 61 (*see Cryptococcus neoformans*)
Trichophyton, 102, 103, 104, 110, 115
Trichophyton gypseum, 107
Trichophyton mentagrophytes, 103, 107, 110, 111, 112, 114
Trichophyton purpureum, 108
Trichophyton rubrum, 103, 107, 108, 114
Trichophyton Schoenleini, 104
Trichophyton violaceum, 104
Tuber, 126
Ustilago Leae, 122, 123
- G**
 Genitocrural lesions, 74
 Gentian violet, 78, 79, 80, 83, 84
Geotrichum, 83, 84
 Geotrichosis, 82-84
 diagnosis of, 82, 83
 clinical picture
 bronchitis, 82
 intestinal invasion, 82
 oral lesions, 82
 parenchymal invasion of lungs, 83

- gentian violet in treatment of, 83, 84
- neomycin in treatment of, 84
- prognosis of, 84
- treatment of, 83, 84
- Glossitis, 74
- Grain smuts and rusts, 122, 123
- Gulliermondi, 73
- Gyromitra esculenta*, 128
- ## II
- Hair and scalp, infections of, 103-104, 115, 116
- Hairs, infected by *Microsporum* dermatophytes fluoresce, 109
- Hands, infections of, 105
- Headache, symptom in cryptococcosis, 63
- Heart, pulmonary actinomycosis in, 9
- Helminths, 4
- Hepatomegalia, in histoplasmosis, 45
- Histoplasma capsulatum*, 34, 40, 41, 42, 43, 44, 45, 46
- Histoplasmosis, 40-50
- abscess formations in, 44
 - anemia in, 45
 - asymptomatic pulmonary form, 42
 - benign pulmonary type of, 41, 42, 43
 - clinical picture of, 42
 - diagnosis of, 42-47
 - disseminated type, 45
 - erythema, 40
 - hepatomegaly, 40
 - lymphadenopathy, 40
 - purpura, 40
 - splenomegaly, 40
 - ulcers of nose, mouth and throat, 40
 - ulcerative enteritis, 40
 - urticaria, 40
 - erythema in, 45
 - ethyl vanillate in treatment of, 47, 48
 - heptomegalia in, 45
 - involvement of reticuloendothelial system, 41
 - irregular fever in, 41
 - leukopenia in, 45
 - lymphadenopathy in, 45
 - mycology of, 45, 46
 - primary muco-cutaneous type, 40, 44
 - purpura in, 45
 - regional lymphadenitis in, 44
 - septic fever in, 45
 - skin and serological tests in, 46
 - splenomegalia in, 45
 - sulfadiazine in treatment of, 47
 - symptomatic pulmonary form, 43
 - thrombocytopenia in, 45
 - treatment of, 47, 49
- Hodgkin's disease and cryptococcosis, 66, 67
- Hormodendrum*, 87, 118, 119, 120, 121
- Hydatid cyst, 66
- Hyperhydrosis in dermatophytosis, 105
- Hyperkeratosis, 112, 113
- Hyperthermia, in treatment of cryptococcosis, 70
- Hypersensitivity
- in blastomycosis, 33, 34, 35
 - in coccidioidomycosis, 23, 24, 26
 - in dermatophytosis, 109, 110, 111
 - in histoplasmosis, 42, 45, 46
 - in moniliasis, 77, 78
 - of infections, 109
 - tuberculin type, 109
- Hyphomycetes, cause of mycetoma pedis, 15
- Hypochromic anemia, 33

- Phycomyces*, 3
Claviceps purpurea, 127, 128
Coccidioides immitis, 21-28, 91
Cryptococcus neoformans, 61
 disease provoking, ■
Ectothrix Trichophyton, 102
Endothrix Trichophyton, 102
Epidermophyton, 102, 103, 106
Epidermophyton floccosum, 103,
 105, 106, 109
Epidermophyton inguinale, 109
 ergot, 4
Geotrichum, 82, 83, 84
 growth of, 3
Gyromitra esculenta, 126
Histoplasma capsulatum, 40, 41
Hormodendrum, 87, 118, 119,
 120, 121
 Imperfecti, 4
Microsporum, 102, 103, 104, 106,
 108-116
Microsporum Audouini, 103, 104,
 108, 115
Microsporum canis, 103, 104,
 108
Microsporum felineum, 108
Microsporum gypseum, 104, 107,
 108, 109, 115
Microsporum lanosum, 108
Monilia, 73, 111 (see *Candida*)
Monilia albicans, 73 (see *Candi-*
 da albicans)
Morchella, 126
Mucor, 4, 95, 118, 119, 122
Mucor corymbifer, 98
Mucor rhizopodiformis, 98
Nocardia asteroides, 14, 15
Nocardia madurae, 13, 16
Nocardia Mexicana, 13, 16
 nonpathogenic, 3
 oidiomycum, 111
Oidium, 111 (see *Candida*)
Paracoccidioides brasiliensis, 91
Penicillia, 120
Penicillium, 95, 118, 119, 120
Phialophora compactum, 86, 88
Phialophora Pedrosi, 86, 88
Phialophora verrucosa, 86, 87,
 88
 poisonous, 124-128
Puccinia graminis, 123
Rhizopus, 4, 95, 99, 119, 122
Rhizopus nigricans, 122
 rodents as reservoirs for, ■
 saprophytic, 3, 119
Serratia marcescens, 27
 spores of saprophytes as allerg-
 ens, 118-123
Sporothrix Schenckii, 53
Sporotrichum Beurmanni, 53
Sporotrichum Schenckii, 53
Torula histolytica, 61 (see *Cryp-*
 tococcus neoformans)
Trichophyton, 102, 103, 104,
 110, 115
Trichophyton gypseum, 107
Trichophyton mentagrophytes,
 103, 107, 110, 111, 112,
 114
Trichophyton purpureum, 108
Trichophyton rubrum, 103, 107,
 108, 114
Trichophyton Schoenleini, 104
Trichophyton violaceum, 104
Tuber, 126
Ustilago Leae, 122, 123
- G**
 Genitocrural lesions, 74
 Gentian violet, 78, 79, 80, 83, 84
 Geotrichum, 83, 84
 Geotrichosis, 82-84
 diagnosis of, 82, 83
 clinical picture
 bronchitis, 82
 intestinal invasion, 82
 oral lesions, 82
 parenchymal invasion of lungs,
 83

- Microsporium*, 102, 103, 104, 106, 108-116
Audouinii, 103, 104, 108, 115
canis, 103, 104, 108
dermatophytes fluoresce, 109
felinum, 108
gypseum, 104, 107, 108
lanosum, 108
- Molds
 concentration of, 118
 grain, 122, 123
- Monilia*, 73, 111 (*see Candida*)
albicans, 73
- Moniliasis, 72-81
 allergic eczema in, 78
 antibiotics, reaction from, 73
 bronchial asthma in, 77, 78
 caprylic compound, N.N.R. in treatment of, 80
 clinical picture, 76
 bronchopulmonary, 76
 endocarditis, 77
 infection of intestinal tract, 81
 infection of mucous membranes of mouth (thrush), 75
 infection of mucous membranes of vagina, 75
 infection of nails, 76
 infection of skin, 75
 meningitis, 77
 pulmonary, 77
 systemic infection, 77
 diagnosis of, 75-79
 differential diagnosis
 in North American blastomycosis, 30
 eczematoid dermatitis in, 78
 gentian violet in treatment of, 78
 methylrosaniline chloride N.F.
 in treatment of, 79, 80
 mycology of, 78, 79
 naprylate in treatment of, 79, 80
 nystatin in treatment of, 81
 potassium iodide in treatment of, 80
 potassium permanganate in treatment of, 80
 skin and serological tests in, 78
 sodium caprylate in treatment of, 79, 80
 treatment of, 79, 80
 urticaria in, 78
- Morbilliform rash, 23
- Morchella*, 126
- Mouth
 cryptococcosis of, 67
 geotrichosis of, 82
 histoplasmosis of, 44
 infection of mucous membranes in moniliasis, 75
 South American blastomycosis of, 92
 thrush, 75
- Mucor*, 4, 95, 118, 119, 122
corymbifer, 98
rhizopodiformis, 98
- Mucoraceae, 99
- Mucormycosis, 98-100
 diagnosis of, 98
 mycology of, 99
 treatment of, 99
- Mushroom poisoning, (*see Mycetismus*)
- Mycetismus, 124-127
 symptoms, 125
 treatment, 126, 127
 delayed type, 126, 127
 rapid type, 127
- Mycetoma pedis* (Madura foot), 15
 diagnosis of, 15, 16
 treatment of, 16, 17
- Mycobacteriaceae, 5
 genus *Mycobacterium*, 5
- Mycology of
 actinomycosis, 10
 aspergillosis, 95, 96
 chromoblastomycosis, 89

I

- Ichthyol, 112
 Imperfect, fungi, 3
 mycelium of ascomycetes and, 4
 Influenza and coccidioidomycosis, 20

Intestinal tract,

- actinomycosis in, 11
 geotrichosis in, 82
 histoplasmosis in, 40
 moniliasis in, 81

Iodides, in treatment of

- actinomycosis, 11
 aspergillosis, 98
 chromoblastomycosis, 89
 cutaneous blastomycosis, 35
 geotrichosis, 84
 moniliasis, 80
 pulmonary blastomycosis, 86
 sporotrichosis, 57, 58

J

- Jacksonian epilepsy, 64
 Joints and bones, infections of, 9, 25, 33, 67

K

- Kidneys, abscesses of, 33
 Krusei, 73

L

- Leucocytosis, 7, 9, 13, 20, 30
 Leukopenia in histoplasmosis, 45
 Liver, abscesses of, 9, 33
 Lungs
 actinomycosis in, 8
 aspergillosis in, 95
 blastomycosis in, 32
 coccidioidomycosis in, 23, 25
 cryptococcosis in, 63, 65
 geotrichosis in, 82
 histoplasmosis in, 42, 43
 moniliasis in, 77
 mucormycosis in, 98
 nocardiosis in, 14

 roentgenograms of, in diagnosis, 32, 65

 sporotrichosis, 55

Lymphadenitis, regional in histoplasmosis, 44

Lymphadenopathy, 40

 in chromoblastomycosis, 88

 in cryptococcosis, 60

 in histoplasmosis, 45

 in sporotrichosis, 55

Lymph glands

 infection in, 86, 87

 South American blastomycosis in, 92

M

- Madura foot, 15
 Magnesium sulfate, 126
 Measles, 20
 Mediastinal glands, enlargement of, 25, 32
 Mediastinum
 actinomycosis in, 8, 9
 blastomycosis in, 32
 Meningitis, 25, 60, 65, 77
 Meningo-encephalitis, 64
 Metacresyl acetate, 96
 Methylrosaniline chloride (*see* Gentian violet)

Microscopic examinations in

- actinomycosis, 7
 aspergillosis, 96
 chromoblastomycosis, 86
 coccidioidomycosis, 20
 cryptococcosis (*torulosis*), 60
 dermatophytosis, 107, 108, 109
 histoplasmosis, 40
 moniliasis, 72
 nocardiosis, 13
 North American blastomycosis, 30
 South American blastomycosis, 90
 sporotrichosis, 52

- Oidium*, 111
Onychia, 76
 treatment of, 80
 Oral lesions (*see* mouth)
Osteomyelitis
 differential diagnosis in
 actinomycosis, 7
 North American blastomycosis,
 30
Ovaries, actinomycosis in, 11
- P**
Paracoccidioides brasiliensis, 91
Paracoccidioidin, 92
Parakrusci, 73
Paranasal sinuses
 actinomycosis in, 8
 aspergillosis in, 95
Parenchymal invasion of lungs
 (*see* Lungs)
Paronychia, 76, 98
Pectinate hyphae, 107, 108, 109
Pedis, 103, 105
Penicillia, characterization of, 120
Penicillin, 16
 allergic reactions to, 110
Penicillium, 95, 118, 119, 120
Pericardium, pulmonary actinomy-
 cosis in, 9
Perlèche, 74
Phialophora
 compactum, 86, 88
 Pedrosoi, 86, 111
 verrucosa, 86, 87, 88
Phlyctenular conjunctivitis, 23
Phycomycetes fungi, 3, 4
Pneumonia, 20
 "Pneumonitis of unknown eti-
 ology," 43
Poisonous fungi, 124-128
Poliomyelitis, 20
Potassium iodide in treatment of
 actinomycosis, 11
 aspergillosis, 96
 chromoblastomycosis, 89
 cutaneous blastomycosis without
 allergy, 35
 geotrichosis, 111
 moniliasis, 80
 pulmonary blastomycosis, 36
 sporotrichosis, 57, 58
Potassium permanganate in treat-
 ment of
 dermatophytosis, 112
 moniliasis, 80
Primary muco-cutaneous type of
 histoplasmosis, 41
Prodigious in treatment of cocci-
 doidomycosis, 27
Prodromal morbilliform rash, 20
Prognosis of
 aspergillosis, 96
 coccidioidomycosis, 27
 cryptococcosis, 69
Progressive coccidioidomycosis, 24,
 25
Propamidine, 37
Propionic acid ointment, 112
Protozoa, 4
Protozoan infection, 22
Pruritus, anal, 74
Pruritus, vulval, 74
Pseudotropicalis, 73
Puccinia graminis, 123
Pulmonary actinomycosis, 11
Pulmonary aspergillosis, 95, 96
Pulmonary blastomycosis, 35
Pulmonary coccidioidomycosis, 23,
 25
Pulmonary cryptococcosis, 60
Pulmonary histoplasmosis, 42, 43
Pulmonary moniliasis
 diagnosis of, 77
 treatment of, 80
Pulmonary mucormycosis, 98
Pulmonary nocardiosis, 14, 15
Pulmonary sporotrichosis, 55
Pulmonary tuberculosis, 14, 15
Purpura, 40
 in histoplasmosis, 45

- coccidioidomycosis, 26
- cryptococcosis, 63, 69
- dermatophytosis, 106-111
- geotrichosis, 83
- histoplasmosis, 45
- moniliasis, 78
- mucormycosis, 99
- nocardiosis, 16
- North American blastomycosis, 33
- South American blastomycosis, 92
- sporotrichosis, 56
- Mycoses
 - cause of deaths in United States, 4
- Mycotic endocarditis in moniliasis, 77
- N
- Nails
 - infection of, 106
 - in dermatophytosis, 114
 - in moniliasis, 76
- Naprylate, 79, 80
- Neck, actinomycosis in, 8
- Neomycin, 84
- Neoplasm
 - differential diagnosis in actinomycosis, 7
 - North American blastomycosis, 30
- Nocardia asteroides*, 13, 14
 - produces caseating type of bronchopneumonia, 14
- Nocardia madurae*, 13, 16
- Nocardia Mexicana*, 13, 16
- Nocardiosis
 - definition of, 12
 - diagnosis of, 14, 15
 - differential diagnosis in actinomycosis, 7
 - drugs in treatment of
 - sureomycin, 17
 - penicillin, 16
 - sulfadiazine, 16
 - sulfamerazine, 17
 - mycology of, 16
 - treatment of, 16, 17
- Nonpathogenic fungi, 3, 119
- North American blastomycosis, 30-39
 - areas found in, 31
 - characterization of, 31
 - clinical picture of, 32
 - complement-fixation test for, 34, 35
 - contagious, 31
 - cutaneous, with allergy, 35
 - cutaneous, without allergy, 35
 - diagnosis of, 32-34
 - differential diagnosis in
 - actinomycosis, 30
 - coccidioidomycosis, 30
 - cryptococcosis, 30
 - moniliasis, 30
 - neoplasm, 30
 - osteomyelitis, 30
 - sarcoidosis, 30
 - silicosis, 30
 - sporotrichosis, 30
 - syphilis, 30
 - tuberculosis, 30
 - mycology of, 33
 - propamidine in treatment of, 37
 - skin and serological tests in, 30, 33
 - stilbamidine in treatment of, 37
 - neuropathy in, 37
 - symptoms of, 31
 - systemic, 32
 - technique of desensitization therapy in, 35
 - treatment of, 35-38
 - x-ray in treatment of, 36
- Nystatin, 81
- O
- Oxidomycin, 111

- Sodium caprylate, N.N.R., 79, 80
 Sodium iodide, 57, 58, 89
 Sodium pentobarbital, 127
 Soproinol, 112, 113, 115, 116
 South American blastomycosis, 90-93
 diagnosis of, 91, 92
 in lymph glands, 92
 microscopic examination of, 90
 mycology of, 92
 skin and serological tests in, 92
 sulfadiazine in treatment of, 93
 sulfamerazine in treatment of, 93
 treatment of, 93
 "Spherules," 26
 Spleen, abscesses of, 33
 Splenomegalia in histoplasmosis, 45
 Splenomegaly, 40
 Spores of saprophytic fungi as allergens, 118-123
Sporothrix, 53
 Schenckii, 53, 55
Sporotrichum, 53
 Beurmanni, 53
 Schenckii, 53
 Sporotrichosis, 52-58
 acneiform type, 52, 58
 areas found in, 54
 clinical picture of, 54, 55
 diagnosis of, 54, 55
 differential diagnosis in
 actinomycosis, 7
 nocardiosis, 13
 North American blastomycosis, 30
 discovery of, 53
 epidemic of, 54
 in cryptococcosis, 67
 iodides in treatment of, 57, 58
 localized lymphatic type of, 52
 mycology of, 56
 potassium iodide in treatment of, 57, 58
 prognosis of, 55
 skin tests of, 57
 sodium iodide in treatment of, 57, 58
 treatment of, 57, 58
 St Anthony's Fire, 128
Stellatoidea, 73
Stilbamidine, 37
 Stomatitis, 74
 Streptomycetaceae
 genus *Micromonospora*, 5
 genus *Streptomyces*, 11
 Sulfadiazine in treatment of
 actinomycosis, 11
 histoplasmosis, 47
 nocardiosis, 16
 South American blastomycosis, 93
 Sulfamerazine in treatment of
 actinomycosis, 11
 nocardiosis, 17
 South American blastomycosis, 93
 Sulphur granules
 in diagnosing actinomycosis, 10
 of mycetoma pedis, 16
 Syphilis, 7, 30, 67
 Systemic blastomycosis, management of, 35
 Systemic infection in moniliasis, 77
- T**
 Taxonomy, 5
 Thrombocytopenia in histoplasmosis, 45
 Thrush mouth, 75
 Timofax, 112
 Tinea
 barbae, 103
 capitis, 103
 corporis, 104
 cruris, 104
 pedis, 105
 unguium, 106
Torula histolytica, 61
Torulosis, 60-71

R

Racquet mycelium, 107, 108, 109

Rash

morbilliform, 23

prodromal morbilliform, 20

Regional lymphadenitis, 41 (*see*
Lymphadenopathy)

Respiratory system, infection of, 8,
14, 23, 25, 32, 42, 43, 55,
63, 65, 66, 77, 82, 95, 98

Reticuloendothelial system in his-
toplasmosis, 41

Rheumatism, desert, 21

Rhizopus, 4, 95, 99, 119, 122

nigricans, 122

Rickettsiae, 4

Roentgenograms (*see also* X-ray)
in bronchopulmonary moniliasis,
76

in diagnosis of cryptococcosis,
65, 66, 67

of lungs

in coccidioidomycosis, 23

in histoplasmosis, 42, 43

in North American blasto-
mycosis, 32

pulmonary in geotrichosis, 83

S

Sabouraud's medium, 26, 30, 33,
60, 68

Saccharomyces, 31

Saint Anthony's Fire, 128

Salicylanilide, 115, 116

Salicylic acid ointment, 114

Salivary glands, actinomycosis in, ■

San Joaquin fever, 21, 22

Saprophytic fungi, 3, 119

Sarcoidosis, 30, 66

Scalp and hair, infections of, 103-
104, 115, 116

Scarlet fever, 20

Sclerotium, 127

Sedimentation rate in laboratory
studies of

actinomycosis, 7

coccidioidomycosis, 20, 24

nocardiosis, 13

North American blastomycosis,
30, 33

Serratia marcescens, 27

Silicosis, 30

Skin

and mucous membranes, 44, 67,
75, 82, ■■

and serological tests in

actinomycosis, 10, 11

aspergillosis, 96

chromoblastomycosis, 88, 89

coccidioidomycosis, 23

cryptococcosis, 69

dermatophytosis, 109, 110, 111

histoplasmosis, 46

moniliasis, 78

North American blastomy-
cosis, 33

South American blastomy-
cosis, 92

sporotrichosis, 57

infections of in

chromoblastomycosis, 87

coccidioidomycosis, 25

cryptococcosis, 67

dermatophytosis, 104, 105

histoplasmosis, 44

moniliasis, 75, 76

mucormycosis, 98

North American blastomy-
cosis, 32

South American blastomy-
cosis, 91

sporotrichosis, 54, 56

lesions

erythema multiforme, 21

erythema nodosum, 21

purpura, 45

urticaria, 45

verrucous, 25

treatment of, in dermatophytosis,
112

NAME INDEX

- Abrahmas, I , 70, 71
 Aird, J A , 53, 58
 Ajello, L , 42, 49, 79, 81
 Alexander, E. II , 50
 Ashe, B L , 84

 Beadenkopf, W G., 42, 50
 Beidleman, B., 84
 Bendove, R A., 84
 Benham, R W., 61, 70
 Berk, M , 70, 71
 Brumpt, E., 87, 88
 Buschke, A , 61, 70
 Busse, O , 61, 70

 Carter, H V , 15, 18
 Castellani, A , 98, 99
 Christie, A , 41, 47, 49, 50
 Clancy, C. F., 84
 Colbert, J. W , Jr , 37, 38
 Collins, B E., 94, 97
 Conant, N F , 33, 38, 91, 93
 Crispell, L. III , 42, 49
 Curtis, A C , 37, 39
 Cutler, E. C , 61, 71

 Darling, S T., 41, 49
 Davis, D. J , 53, 58
 de Almeida, F , 93
 de Beurmann, L , 53, 58
 Décourt, L V., 93
 De Moubreun, W A , 41, 49
 Dickson, E C , 22, 28
 Drake, C. H , 6, 17
 Dubos, René J , 71, 74, 81
 Duncan, G. G , 84

 Elmore, F. H , 26, 28

 Elson, W O , 37, 38
 Emmons, C W , 14, 18, 42, 49,
 62, 71
 Erickson, D , 6, 17
 Erksen, N , 34, 38
 Ernst, H C , 98, 99

 Feldman, H A , 43, 50
 Fink, J C , 37, 39
 Florey, H W , 11, 17
 Florey, M E , 11, 17
 French, E C , 42, 49
 Furcolow, M L , 42, 49, 50
 Fusillo, M H , 11, 17

 Gammel, J A , 15, 18
 Gerstl, B , 70, 71, 95, 97
 Gifford, M A , 22, 28
 Gilchrist, T C , 22, 28, 31, 38
 Gill, K , 94, 96
 Gill, W D , 94, 96
 Ginsberg, M , 37, 38
 Goblin, M , 95, 97
 Golden, A , 93, 100
 Gomez, J M , 87, 89
 Gougerat, II , 53, 58
 Graham, H , 98, 99
 Grayston, J T , 42, 49, 50
 Green, P , 42, 50
 Green, R H , 37, 38
 Greenspan, E M , 37, 38
 Gregory, J III , 98, 100

 Harrell, III R , Jr , 37, 39
 Harris, M M , 94, 97
 Haymaker, W., 98, 100
 Hektoen, L , 53, 58
 Henricl, A. T., 5, 17

Treatment of

- actinomycosis, 11
- aspergillosis, 98
- chromoblastomycosis, 89
- coccidioidomycosis, 27
- cryptococcosis, 69, 70
- dermatophytosis, 111-116
- geotrichosis, 83, 84
- histoplasmosis, 47
- moniliasis, 79, 80
- mucormycosis, 99
- mycetismus, 126, 127
- nocardiosis, 16, 17
- North American blastomycosis, 35-38
- South American blastomycosis, 93
- sporotrichosis, 57, 58
- Trichophyton, 109, 110
- Trichophyton*
 - ectothrix, 102
 - endothrix, 102
 - fungi, 110
 - gypseum*, 107
 - mentagrophytes*, 103, 107
 - mycology of, 107
 - purpureum*, 108
 - rubrum*, 103, 107, 108, 114
 - Schoenleini*, 104
 - violaceum*, 104
- Tropicalis*, 73
- Truffles, 126
- Tuber*, 126
- Tubercle bacillus, 42
- Tuberculin cross reaction with
 - asteroidin, 14
- Tuberculin type hypersensitivity, 109
- Tuberculosis
 - differential diagnosis in
 - actinomycosis, 7
 - coccidioidomycosis, 20

cryptococcosis, 67

nocardiosis, 13

North American blastomycosis, 30

Tuberculous meningitis, 25

Tularemia, 7

U

Ulcerative ententis, 40

Ulcers in

mouth, 40

nose, 40

throat, 40

Undecylenic acid ointment, 112

Unguam, 103, 106

Urticaria, 40

in moniliasis, 78

Ustilago *Leae*, 122, 123

V

Vagina, infection in, 75, 76

Valley fever, 21

Vulval pruritus, 74

W

Whitfield's ointment, 118

"Wood's Light," 109, 115

X

X-ray (*see also* Roentgenograms)

in treatment of

actinomycosis, 12

chromoblastomycosis, 89

cryptococcosis, 70

cutaneous blastomycosis, 35

dermatophytosis (scalp and hair), 115

moniliasis, 80

North American blastomycosis, 36

Z

Zinc oxide ointment, 112

NAME INDEX

- Abrahamas, I , 70, 71
 Aird, J A , 53, 58
 Ajello, L., 42, 49, 79, 81
 Alexander, E. R. , 50
 Ashe, H I , 84

 Beadenkopf, W G , 42, 50
 Beidleman, H , 84
 Bendove, R A., 84
 Benham, R W , 61, 70
 Berk, M , 70, 71
 Brumpton, E , 87, 89
 Buschke, A., 61, 70
 Busse, O , 61, 70

 Carter, H V , 15, 18
 Castellani, A , 98, 99
 Christie, A , 41, 47, 49, 50
 Clancy, C F , 84
 Colbert, J W , Jr , 37, 38
 Collins, B E , 94, 97
 Conant, N F., 33, 38, 91, 93
 Crispell, L S , 42, 49
 Curtis, A. C , 37, 88
 Cutler, E C , 61, 71

 Darling, S T , 41, 49
 Davis, D J , 53, 58
 de Almeida, F , 93
 de Beurmann, L. , 53, 58
 Décourt, L V., 93
 De Monbreun, W A , 41, 49
 Dickson, E C , 22, 28
 Drake, C H , 6, 17
 Dubos, René J , 71, 74, 81
 Duncan, C G , 84

 Elmore, F. H , 26, 28

 Elson, W O , 37, 38
 Emmons, C. W , 14, 18, 42, 49,
 62, 71
 Enckson, D , 6, 17
 Enksen, N , 34, 38
 Ernst, H C , 98, 99

 Feldman, H A , 43, 50
 Fink, J C , 37, 39
 Florey, H W , 11, 17
 Florey, M E , 11, 17
 French, E E , 42, 49
 Furcolow, M L , 42, 49, 50
 Fusillo, M H , 11, 17

 Gammel, J A , 15, 18
 Gerstl, B , 70, 71, 95, 97
 Gifford, M A , 22, 28
 Gilchrist, T C , 22, 28, 31, 38
 Gill, K., 94, 96
 Gill, W D , 94, 96
 Ginsberg, M , 37, 38
 Goblun, M , 95, 97
 Golden, A , 98, 100
 Gomez, J M , 87, 89
 Cougerat, E , 53, 58
 Graham, H , 98, 99
 Grayston, J T., 42, 49, 50
 Green, P , 42, 50
 Green, R H , 37, 38
 Greenspan, E M , 37, 88
 Gregory, J E., 98, 100

 Harrell, E. R. , Jr , 37, 39
 Harris, M. M , 94, 97
 Haymaker, W , 93, 100
 Hektoen, L , 53, 58
 Henriel, A T , 5, 17

Treatment of

- actinomycosis, 11
- aspergillosis, 96
- chromoblastomycosis, 89
- coccidioidomycosis, 27
- cryptococcosis, 69, 70
- dermatophytosis, 111-116
- geotrichosis, 83, 84
- histoplasmosis, 47
- moniliasis, 79, 80
- mucormycosis, 99
- mycetismus, 126, 127
- nocardiosis, 16, 17
- North American blastomycosis, 35-38
- South American blastomycosis, 93
- sporotrichosis, 57, 58
- Trichophyton, 109, 110
- Trichophyton*
 - ectothrix, 102
 - endothrix, 102
 - fungi, 110
 - gypseum*, 107
 - mentagrophytes*, 103, 107
 - mycology of, 107
 - purpureum*, 108
 - rubrum*, 103, 107, 108, 114
 - Schoenleini*, 104
 - violaceum*, 104
- Tropicalis*, 73
- Truffles, 126
- Tuber, 126
- Tubercle bacillus, 42
- Tuberculin cross reaction with
 - asteroidin, 14
- Tuberculin type hypersensitivity, 109
- Tuberculosis
 - differential diagnosis in
 - actinomycosis, 7
 - coccidioidomycosis, 20

- cryptococcosis, 67
- nocardiosis, 13
- North American blastomycosis, 30

- Tuberculous meningitis, 25
- Tularemia, 7

U

- Ulcerative enteritis, 40
- Ulcers in
 - mouth, 40
 - nose, 40
 - throat, 40
- Undecylenic acid ointment, 112
- Unguim, 103, 106
- Urticaria, 40
 - in moniliasis, 78
- Ustilago Leae*, 122, 123

V

- Vagina, infection in, 75, 76
- Valley fever, 21
- Vulval pruritus, 74

W

- Whitfield's ointment, 113
- "Wood's Light," 109, 115

X

- X-ray (*see also* Roentgenograms)
 - in treatment of
 - actinomycosis, 12
 - chromoblastomycosis, 89
 - cryptococcosis, 70
 - cutaneous blastomycosis, 35
 - dermatophytosis (scalp and hair), 115
 - moniliasis, 80
 - North American blastomycosis, 36

Z

- Zinc oxide ointment, 112

- Sporer, A., 16, 18
Sprunt, D. H., 11, 17
Stoddard, J. L., 61, 71
Stokes, W. R., 31, 38
Strauss, M. J., 37, 38
Strauss, H. E., 17, 18
Symmers, B., 16, 18

Thompson, L., 6, 17

VanderPloeg, D. E., 37, 39

Vaughan, J. E., 25, 28

Wade, J. L., 98, 100
Waksman, S. A., 5, 17
Watjen, J., 98, 99
Weidman, W. H., 95, 97
Weld, Julia T., 79, 81
Wernicke, R., 22, 28
Wolgamot, J. R., III
Wood, Robert, 109

Zeidberg, L. D., 42, 49

- Herrell, W. E., 11, 17
 Hertzog, A. J., 95, 97
 Hetherington, L. H., 95, 97
 Hillegas, A. B., 11, 17
 Howell, A., 91, 93

 Jacobson, H. P., 27, 28
 Jillson, O. F., 42, 49

 Kapros, C. E., 70, 71
 Keeney, E. L., 34, 38, 57, 58, 78, 81
 Kessell, J. F., 24, 28
 Kirby, W. M. M., 14, 17, 18
 Khigman, A. M., 17, 18, 41, 49, 74, 76, 81
 Korns, 43, 50
 Kurung, J. M., 42, 49

 Lacaz, C. da S., 93
 Lack, A., 27, 88
 Lack, H., 42, 50
 Lane, C. G., 87, 89
 Larsh, H. W., 43, 50
 Levy, E. D., 37, 39
 Lichtheim, L., 98, 99
 Lepnik, M. J., 74, 81
 Littman, M. L., 11, 17
 Livingood, C. S., 76, 81
 Long, P. H., 37, 38
 Loosli, C. G., 42, 50
 Lutz, A., 91, 93

 Martin, D. S., 34, 38
 Matthews, A. R. E., 98, 100
 McCoy, J. F., 47, 50
 McLean, I. W., Jr., 11, 17
 McNaught, J. B., 14, 18
 McVay, L. V., Jr., 11, 17
 McVickar, D. L., 47, 50
 Medlar, E. M., 87, 89
 Meyer, K. F., 53, 58
 Middleton, J. G., 47, 50
 Miller, J. M., 37, 38
 Minchew, B. H., 94, 97

 Minot, Ann S., 43
 Moffitt, H. C., 22, 28
 Monteiro de Barros, O., 93
 Monroe, J., 42, 49
 Moursund, M. F., 37, 39

 Nauen, R., 43, 50
 Neill, J., 70, 71
 Negroni, P., 88
 Neto, M. R., 93
 Newmann, A. V., 95, 97
 Nichols, D. R., 11, 17

 Ophuls, W., 22, 28

 Palmer, C. E., 41, 49
 Pariser, H., 37, 39
 Paul, J. S., 17
 Pearl, I. A., 47, 50
 Pedroso, A., 87, 89
 Perkins, C. F., 53, 58
 Petersen, J. C., 41, 47, 49, 50
 Phillips, G. E., 11, 17
 Pillsbury, D. M., 17, 18, 41, 49
 Posada, A., 22, 28
 Poulton, E. P., 11, 17

 Ramirez, H., 25, 28
 Rawson, A. J., 37, 39
 Rice, F. A., 42, 50
 Ruxford, E., 22, 28
 Rosenthal, S. R., 26, 28
 Routien, J. B., 26, 28

 Sabin, A. H., 43, 47, 50
 Savage, L. J., 50
 Schenck, B. H., 53, 53
 Schlingman, H., 17
 Schoenbach, E. B., 37, 38
 Schwab, H., 17
 Silva, M., 54, 58
 Slattery, R. V., 42, 50
 Smith, C. E., 23, 26, 28
 Smith, D. T., 31, 34, 38
 Smith, T. S., 95, 97

- Sporer, A , 16, 18
Sprunt, D H , 11, 17
Stoddard, J. L. , 61, 71
Stokes, W. R., 31, 38
Strauss, M J , 37, 38
Strauss, R E , 17, 18
Symmers, D , 16, 18

Thompson, L., 6, 17

VanderPloeg, D E , 37, 39

Vaughan, J E , 25, 28

Wade, J. L. , 98, 100
Waksman, S. A , 5, 17
Watjen, J. , 98, 99
Weidman, W H , 95, 97
Weld, Julia T., 79, 81
Wernicke, R , 22, 28
Wolgamot, J R , 84
Wood, Robert, 109

Zeidberg, L B , 42, 49

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By

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